Diagnosing tubal pathology: The individual approach
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Individual patient data meta-analysis; a promising approach for evidence synthesis in reproductive medicine

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Abstract

Systematic reviews and accompanying meta-analyses are the cornerstones of evidence based medicine. Systematic reviews summarize clinical evidence; meta-analyses provide summary estimates of treatment effect or diagnostic test accuracy. Although deemed to provide the highest level of evidence, their clinical value is limited as they can only summarize aggregated data. In these meta-analyses the true variability of the treatment effects can not be explored to the desired extent, because the meta-analyses cannot distinguish between patients with different clinical profiles. Systematic reviews and meta-analyses based on individual patient data (IPD), described as the ‘gold standard’ for systematic reviews, are a promising approach that might overcome these limitations. IPD meta-analyses allow treatment effects and diagnostic accuracy to be estimated at the level of relevant patient subgroups. This enables researchers to investigate effectiveness of treatment in patients with different profiles.

In this article, we address the opportunities of systematic reviews and meta-analyses using individual patient data in reproductive medicine. We discuss its potential based on three clinical examples: single versus double embryo transfer in IVF, the diagnosis of tubal pathology and the prognostic value of ovarian reserve tests. We propose to show potential advantages of IPD systematic reviews and meta-analyses in providing stratified clinical evidence, which could improve medical care.
Introduction

Since the 1980’s, there is a growing consensus that clinical decision making should be supported by judicious and conscientious use of current best evidence from medical care research (Sackett et al., 1985). In view of the steadily growing body of published literature, there is a need to summarize the available knowledge in a systematic and transparent way. At present, systematic reviews and meta-analyses provide the highest level of scientific evidence by summarizing findings published in literature and estimating the overall treatment effect, diagnostic test accuracy or prognostic value (Montori et al., 2003; Sackett et al., 2007).

Conventional systematic reviews and meta-analyses rely on aggregated information. Since there is usually no access to data other than those reported by the original authors, the meta-analyses are restricted by the analyses performed in the original studies, which may be difficult to merge into a summary analysis and it is not possible to perform more detailed analyses, such as analyses of time-to-event data or analyses that take into account patient level covariates (Stewart and Tierney, 2002).

Access to and analysis of original data from the relevant studies could potentially overcome the limitations of conventional meta-analyses and provide the opportunity to integrate patient characteristics into the analyses (Khan et al., 2003; Stewart and Tierney, 2002). This alternative approach to the conventional meta-analysis is called individual patient data (IPD) meta-analysis.

At present, systematic reviews and meta-analyses using individual patient data are rarely used in reproductive medicine. We hypothesize that IPD based systematic reviews and meta-analyses, although yet relatively unknown in the reproductive medicine literature, will become much more frequently used techniques to further improve the quality and clinical usefulness of systematic reviews. In this article we will discuss in more detail the drawbacks of conventional systematic reviews and meta-analyses. We will describe the opportunities and potential pitfalls of systematic reviews and meta-analyses using individual patient data and we will conclude with its applicability in reproductive medicine, both for therapeutic as well as for diagnostic and prognostic research.

Conventional systematic reviews and meta-analyses

Systematic reviews and conventional meta-analyses are established methods for generating high level evidence to support the development of clinical practice guidelines within the arena of evidence based medicine (EBM). They are used to summarize the results of multiple primary studies, allowing a solid base for rational decisions about clinical practice. Such studies could address questions regarding the effectiveness of clinical interventions (randomized clinical trials), the accuracy of diagnostic tests (diagnostic accuracy studies), or of prognostic markers or clinical prediction models (prognostic studies).

In a systematic review, a thorough, computerized search is performed meticulously to detect all studies that could contribute to answer the research question. Studies suitable
for inclusion are then critically examined (preferably by two independent researchers) to see whether they meet specific inclusion criteria. Subsequently, the methodological quality of the included studies is assessed using design-based quality checklists, such as the CONSORT statement for (randomised) clinical trials and QUADAS for diagnostic research (Begg et al., 1996; Khan et al., 2003; Montori et al., 2003; Tseng et al., 2008; Whiting et al., 2003).

Systematic reviews based on randomised clinical trials aim to evaluate the effect of a therapeutic intervention for patients with a specific condition. Reviews of studies of diagnostic test accuracy assess the ability of a test to distinguish between patients with the target condition and patients without the target condition and reviews of prognostic studies investigate associations between risk factors and the occurrence of future events. In meta-analyses of intervention studies the treatment effect is estimated by calculating summary measures of effectiveness, such as relative risk, risk difference or odds ratio, based on pooling the effects of all included studies. In diagnostic and prognostic meta-analyses, the outcome measurements of interest include sensitivity-specificity pairs, predictive values or diagnostic odds ratios. Whether such pooling of outcomes leads to meaningful results, depends on the clinical research question, the included evidence and the total amount of estimated heterogeneity.

**Drawbacks of conventional systematic reviews and meta-analyses**

Conventional systematic reviews and meta-analyses of intervention studies suffer from a number of drawbacks. First, these analyses are -by definition- based on aggregated results, reported in primary studies. Also, as both journals as well as primary investigators are often more likely to publish positive results, this can lead to publication bias in the summary estimates. Studies reported in languages other than English are often excluded. This systematic exclusion of studies can also lead to less accurate or even biased study results (Montori et al., 2003; Stewart and Parmar, 1993).

Second, conventional systematic reviews are dependent on the quality of the primary studies and the way this quality is reported (Stewart and Tierney, 2002).

Third, end points of follow-up in the study might be different than those of primary interest in the review, misleading the study results. The overall treatment effect in a conventional meta-analysis might be overestimated due to the combination of excluded patients, short duration of follow-up and analysis of fixed end-points in the original studies (Stewart and Parmar, 1993).

Finally, the treatment effect may not be identical across patient subgroups. An intervention may be more effective in, say, younger patients and less so in the elderly or vice versa. Yet most studies do not have the power to explore subgroups and only report an overall effect. This can be interpreted as a kind of average effect over all included patient subgroups. In practice, the clinician facing a patient in a clinical setting may be more interested in the subgroup specific effect, not in the average effect (Stewart and Tierney, 2002).
Conventional systematic reviews and meta-analyses of diagnostic accuracy studies face a number of other challenges. First, many diagnostic studies are based on routinely collected data and therefore more susceptible to bias than randomised trials (Rutjes et al., 2006). Second, the most common measure of diagnostic accuracy is the combination of sensitivity and specificity. These vary with the target population, the spectrum of disease, with characteristics of the index test and clinical reference standard and with differences in the threshold for test positivity. Variation in these factors can lead to heterogeneity between studies, complicating the performance of a meta-analysis and decreasing the validity of the summary estimates (Leeflang et al., 2008; Mallett et al., 2006; Virgili et al., 2009). Third, the quality of reporting in many original diagnostic studies is poor. For example, verification and inclusion bias can arise from imprecise definitions of the index test and reference tests and loose criteria for the included population and target disease (Leeflang et al., 2008). Fourth, in clinical practice, a diagnostic work-up may well consist of several combinations of single tests, used in certain sequences. The diagnostic value of the last test in a sequence may then depend on the results of previous tests. Original studies are often not designed to evaluate diagnostic strategies and do not report on selections made in these strategies. Therefore, the value of such diagnostic strategies or pathways cannot be evaluated based on overall accuracy estimates, as currently reported in most diagnostic studies. Also, patient characteristics such as age or disease status are often not integrated in the assessment of overall test accuracy, although the test accuracy may differ across subgroups defined by age or other features. In view of these pitfalls, the results of the conventional diagnostic meta-analyses can only be applied to the average patient and may not be applicable to more stratified diagnostic strategies used in clinical practice (Broeze et al., 2009; Khan et al., 2003; Tatsioni et al., 2005).

Conventional systematic reviews and meta-analyses of prognostic studies face methodological challenges of a different nature. Due to the absence of widely agreed quality criteria most prognostic studies are of low quality and prone to publication bias. Compared to diagnostic meta-analyses, prognostic meta-analyses are also hampered by variations in inclusion criteria, study design, statistical analyses and outcome measurements (Altman, 2001; Hayden et al., 2006).

A potentially more coherent approach to summarizing the evidence from multiple primary studies is to acquire the original data from included studies, and to perform statistical analyses at the individual patient level to obtain summary estimates. We will explore this in the next section.
Systematic reviews and meta-analyses using individual patient data

Some of the drawbacks and biases of conventional systematic reviews and meta-analyses can potentially be resolved by obtaining individual patient data of the original studies provided by the corresponding author.

Outline of systematic reviews and meta-analyses using IPD

The first step in a systematic review based on individual patient data, the selection of eligible studies to answer the detailed research question, does not differ from that of a conventional systematic review. After this selection, corresponding authors of eligible studies are approached by email, letter or telephone and invited to provide the original data to the central analysis group that will perform the IPD meta-analysis. This central analysis group then collects the available data and checks these for inconsistencies with the published results. When data are compatible they are merged together in a single database. The quality of the original studies is carefully evaluated, using quality checklists as the CONSORT statement and QUADAS guideline. The original study authors are contacted to clarify unresolved issues in methods, data or outcomes. The original authors are also invited to identify unpublished or ongoing studies that they are aware of. In this way, unpublished data or follow-up data can be added to the IPD meta-analysis. Imputation can be used for missing data at the individual patient level.

The second step is to establish a central analysis group and an advisory board or steering group, consisting of medical specialists, epidemiologists and statisticians, to discuss planned analyses and preliminary results in detail. After consultation of the advisory board, meetings with the original authors are organized to discuss results of the meta-analysis and any new insights that might have arisen (Simmonds et al., 2005; Stewart and Tierney, 2002).

The third step is to perform statistical analyses. This can be done in a one-stage or on a two-stage approach. In a one-stage approach data from individual studies are pooled together and an overall summary effect is estimated. This approach may adjust to some extent for the heterogeneity in the included studies, e.g. by including study as a fixed effect in the analyses, or by allowing the effects to vary randomly between studies (random effects). In a two-stage approach data are first analysed for each individual study separately. These study-specific estimates are subsequently combined in a conventional meta-analysis to give a summary estimate of the treatment effect. The amount of heterogeneity can be expressed using the I² statistic, similar to conventional meta-analyses. As outcomes of many RCT’s, as well as diagnostic and prognostic research, are dichotomous (mortality, disease status, occurrence of an event), a common statistical method to estimate an overall effect in an IPD meta-analysis is logistic regression modeling.

Access to patient level primary data and increased samples sizes may permit meaningful subgroup analyses. These can be performed by direct selection of specific patient subgroups.
IPD for evidence synthesis in reproductive medicine

or – preferably – by inclusion of patient characteristics as covariates and to estimate interaction effects in a regression model. Sensitivity analyses can be performed, using subsets of studies. Comparison of these results with the results of the complete set of studies may elucidate the impact of study selection on the final outcome (Simmonds et al., 2005; Stewart and Tierney, 2002).

The final step is to report the results in one or more papers. Manuscripts are reviewed by the full collaborative group before submission to a journal and all publications are authored by the collaborative group (Broeze et al., 2009; Simmonds et al., 2005; Stewart and Tierney, 2002).

Advantages of systematic reviews and meta-analyses using IPD

Systematic reviews and meta-analyses of randomised clinical trials that use individual patient data have several potential advantages. First of all, direct contact and collaboration with the original authors has major benefits. These authors are experts on the specific research topic and might be aware of unpublished or ongoing studies. The possibility to include such studies in the systematic review reduces the risk of publication bias. Poor reporting, which is a major problem in all types of research in reproductive medicine, can be counteracted by direct contact with the authors, who can supply the missing or incomplete information on study design or outcomes. Obviously, direct contact with authors is also possible in conventional meta-analysis and is recommended as such by the Cochrane Collaboration.

Second, the availability of the original data and study protocols permits a more detailed assessment of study quality, including methods of randomisation, allocation concealment, and completeness of follow-up. Researchers performing an IPD systematic review of clinical trials are able to assess the method of randomisation from the trial protocols and to further examine the integrity of randomisation by checking for comparability of prognostic factors across treatment arms. Collection of the individual patient data may allow incorporation of follow-up data, enabling estimation of live birth rates instead of pregnancy rates. IPD meta-analysis also allows the inclusion of all randomly assigned patients in the analyses according to the intention to treat principle, even those excluded from analysis in the original trials (Vail and Gardener, 2003; Dias et al., 2006; Chalmers, 1993; Piedbois and Buyse, 2004; Stewart and Parmar, 1993).

Third, access to the original data means that previously inconsistent data can be made compatible and merged into a single database. Examples of this are manifold: continuous results in stead of dichotomized cut-off values can be used or conversions of different assays can be made. Identical, but slightly different defined variables, can be adjusted and analysed together. Imputation assumptions and rules can be made consistent across all studies and the hierarchical nature of subfertility data can be taken into account. In subfertility trials multiple observations per woman, such as multiple treatment cycles, multiple oocytes or multiple embryos, introduce so-called ‘unit of analysis’ errors, since the randomization is based on the included women, but in the analysis the treatment effect is often estimated...
Table I. Overview of advantages & disadvantages of conventional meta-analyses and meta-analyses based on individual patient data.

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<th>Advantages</th>
<th>Conventional meta-analysis &amp; IPD meta-analysis</th>
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<td>Objective approach of summarizing clinical evidence</td>
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<td>Increase sample size</td>
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<td>Increase statistical power of effect</td>
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<td>Estimate heterogeneity</td>
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<td>Generalize conclusions for range of patients</td>
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<td>Analysis continuous data</td>
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<td>Direct contact with trialists</td>
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<td>Feasible for excessive required sample sizes, expensive therapies or logistic problems</td>
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<td>IPD meta-analysis</td>
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<td>Addition of follow-up data</td>
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<td>Time-to-time-event and &quot;sequence&quot; analysis</td>
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<td>Better analysis of subgroup data</td>
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<td>Combination different scales of measurement</td>
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<td>Analysis of differently defined outcome measures</td>
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<td>Allow in-depth exploration of patient factors</td>
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<td>Exploration of the effect of patient exclusions</td>
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<td>Combat poor reporting</td>
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<th>Disadvantages</th>
<th>Conventional meta-analysis &amp; IPD meta-analysis</th>
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<td>Poor quality of reporting original studies</td>
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<td>Problems with incomplete data</td>
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<td>Conventional meta-analysis</td>
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<td>Limited by published analyses</td>
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<td>Overestimation treatment effect</td>
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<td>Patient characteristics not taken into account</td>
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<td>Sequence of tests not taken into account</td>
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<td>Poor adjustment for individual patients</td>
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<td>Poor adjustment for heterogeneity between studies</td>
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<td>IPD meta-analysis</td>
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<td>Time consuming</td>
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<td>Expensive</td>
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<td>Some studies not available for IPD</td>
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<td>Technique is not as well known</td>
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per treatment cycle of per embryo transfer. Using the individual patient data treatment effects or adverse events of treatment, such as ovarian hyperstimulation syndrome, ectopic pregnancies or miscarriages, can be estimated per woman, offering a more valid outcome (Vail and Gardener, 2003; Dias et al., 2006).

Fourth, IPD meta-analysis offers the possibility to perform additional types of analyses. Time to event analyses can be performed for different time points, for example time to recurrence, or time to pregnancy. Different scales of measurements or different outcome measurements can be integrated in the analyses, leading to more extensive use of available data.

Finally, using individual patient data, study-level as well as patient-level factors can be explored and included in the meta-analysis, allowing a more detailed exploration of potential sources of heterogeneity in study results. Analyses can be based on specific subgroups of patients and variations of the summary effect within such patient subgroups can be assessed, allowing a better understanding of the effects of therapy (Bekkering et al., 2009; Stewart and Tierney, 2002).

The full potential of systematic reviews and meta-analyses using IPD in diagnostic accuracy research has yet to be explored, but there are some major theoretical advantages. First, the use of original individual patient data makes it possible to adjust for baseline differences in study design and study populations.

Second, continuous test results can be analysed using the original continuous data values, rather than the dichotomized test values that are generally reported. This increases the amount of information in the analyses and enables the estimation of the most optimal cut off value for the test of interest.

Third, features from the patient’s history and examination, if collected in the original study, can be integrated into the analyses to evaluate the most efficient diagnostic work-up, resulting in a more stratified diagnostic strategy.

Finally, several combinations and sequences of tests can be taken into account and used to perform analyses in which the interactions between test results are integrated (Broeze et al., 2009; Khan et al., 2003).

Although systematic reviews and meta-analyses using IPD are not yet established in prognostic research, they might have potential advantages as well. Access to individual patient data allows the use of more variables, which can then be integrated in multivariable prognostic summary models. Such models may prove to be very valuable in informing patients and in diagnostic and therapeutic decision making (Harrell, Jr. et al., 1996; Steyerberg et al., 2000). For example, in reproductive medicine, the treatment effect and therefore the prognosis of the first period or cycle often affects the participation and treatment choice in subsequent cycles. Also, when pregnancy or live birth occur, treatment stops. In IPD meta-analysis it is possible to take into account the results of the previous cycles when estimating the overall prognosis of subfertility treatment (Vail and Gardener, 2003; Dias et al., 2006).
Challenges of systematic reviews and meta-analyses using IPD

Despite all advantages, systematic reviews and meta-analyses using individual patient data also present some challenges. They can be time consuming, mainly due to efforts required for data acquisition, data extraction and merging, and for getting input from the full collaborative group (Stewart and Tierney, 2002). Comparable to the conventional meta-analytic approach, unpublished studies have to be searched or asked for by the trialists. Researchers of the central analysis group have to create the statistical approach and syntaxes by themselves, since there is still no format of analysis available. Collecting data from original authors can be difficult as study data, especially from older studies, may not have been appropriately archived. Occasionally, the original authors are not traceable and not all authors may be willing to share their data. The summary database may therefore contain only a subset of studies eligible for inclusion and reflect an incomplete coverage of available evidence. Techniques to handle this problem and to estimate a summary effect based on a combination of individual patient data and aggregate level data are currently explored (Clarke et al., 2007; Sutton et al., 2008; Riley et al., 2008; Riley et al., 2008).

Opportunities for systematic reviews and meta-analyses using individual patient data in reproductive medicine

Conventional systematic reviews and meta-analyses in Reproductive Medicine

In reproductive medicine, many systematic reviews and meta-analyses have been published to date; mainly to investigate effects of interventions in infertility and assisted reproduction or to predict pregnancy rates after therapy. Since 1995, around 700 systematic reviews and approximately 35 meta-analyses in the area of reproductive medicine were published in Human Reproduction Update, generating high level scientific evidence.

A systematic review of the association between HLA class II antigens and unexplained recurrent miscarriage demonstrates one of the limitations of conventional meta-analysis (Christiansen et al., 1999). The authors reported that the methodological quality of most included original studies was poor. Further limitations were the small numbers of included patients and the inclusion of patients not corresponding to the definition of recurrent miscarriage. This study shows that it is impossible to estimate a valid overall treatment effect, based on aggregated data, if patients with different definitions of the target disease are included. Two other meta-analyses have the same shortcomings. In a meta-analysis of the effect of therapeutic interventions to restore ovarian function and to achieve pregnancy, the use of the data from the individual studies turned out to be not feasible, because of marked variations in study design, patient selection and mode of intervention (van Kasteren and Schoemaker, 1999). In a meta-analysis on the effect of mild ovarian stimulation for IVF, small sample sizes of single studies and heterogeneity in patient inclusion criteria and outcomes did not allow a meaningful meta-analysis (Verberg et al., 2009).
Ongoing systematic reviews and meta-analyses using individual patient data in Reproductive Medicine

At present, systematic reviews and meta-analyses based on individual patient data in reproductive medicine are still scarce. Although still in its infancy, we will briefly describe three currently conducted systematic reviews and meta-analyses using IPD in reproductive medicine to illustrate the possible advantages of this approach compared to conventional systematic reviews and meta-analyses.

The effectiveness of single versus double embryo transfer (SET resp. DET) in IVF treatment has been addressed in several randomised clinical trials. Two conventional meta-analyses showed a significant decrease in multiple pregnancy rates after IVF with SET (summary OR 0.02 [95 % CI: 0.01 to 0.09] and 0.04 [95 % CI: 0.01 to 0.11]). Live birth rates after SET were halved compared to DET (OR 0.48 [95 % CI: 0.38 to 0.61] and 0.52 [95 % CI: 0.39 to 0.68]) (Gelbaya et al., 2009; Pandian et al., 2005).

In view of this data, the questions arise whether similar livebirth rates can be achieved with SET in women with a good prognosis or whether there are subgroups of patients with such unacceptably high rates of multiple pregnancies with DET that SET is the only safe option. Conventional meta-analyses can not answer these questions, since analyses based on aggregated data are not able to take into account important variables like predictive characteristics of patients and embryos, variations in inclusion criteria, such as upper limits for female age, number of IVF cycles and various drug regimens in IVF protocols (Dare et al., 2004; Gelbaya et al., 2009; Pandian et al., 2005). The use of individual patient data and direct contact with the original authors might be able to overcome these problems to a large extent. Recently, the individual patient data of all eligible RCT’s on this topic were collected, to compare the clinical effectiveness of SET versus DET and to estimate summary odds ratios for live birth rate and multiple birth rate, adjusted for both patient characteristics as well as for laboratory characteristics that may influence the effectiveness of therapy (Harrild et al., 2009). If successful, this IPD project could lead to a valid identification of patient subgroups that will benefit from SET or will be harmed by DET.

A second clinical example of using individual patient data in a systematic review and meta-analysis is in tubal testing in subfertile patients. The diagnosis of tubal pathology is usually based on results of the Chlamydia antibody test (CAT), hysterosalpingography (HSG) and diagnostic laparoscopy.

A conventional meta-analysis of the diagnostic accuracy of the Chlamydia antibody test (CAT) showed a strong variation in overall accuracy; with sensitivity estimates ranging from 21% to 90%, and specificity estimates from 29% to 100%, depending on the type of assay used (Mol et al., 1997). The summary estimate of HSG accuracy showed a sensitivity of 65% with a specificity of 83% (Swart et al., 1995).

The assumption that these accuracies are stable across patient subgroups has never been tested explicitly. It may well be that in some groups of patients the accuracy of these tests is so poor that the tests should not be performed in these patients. There is only one
conventional systematic review that systematically identified possible risk indicators in the medical history for tubal pathology, but multivariable analyses could not be performed, as the construction of 2x2 tables per risk indicator did not allow correcting for their mutual dependence (Luttjeboer et al., 2009).

In view of the limitations of these conventional meta-analyses, there is still no consensus on which test should be used initially in the diagnostic work-up, in which sequence additional tests should be performed and what cut-off values should be used.

Individual patient data meta-analyses may allow for the integration of different definitions of tubal pathology, of different CAT assays, studying several sequences of tests and continuous test results and risk indicators, based on both clinical history and physical examination. IPD meta-analyses could generate data leading to a more stratified diagnostic strategy. A study protocol, in which a systematic review and meta-analysis based on individual patient data concerning the diagnosis of tubal pathology is described in more detail, has been published recently (Broeze et al., 2009).

A third clinical example of an IPD systematic review and meta-analysis, currently under way, is the predictive value of ovarian reserve tests for IVF outcome (van Disseldorp et al., 2009).

Several ovarian reserve tests (ORT’s) have been used to predict outcome of IVF outcome in terms of oocyte yield or pregnancy rates. Based on these tests couples are counselled on their pregnancy chances prior to IVF, and individual dose adjustments are often suggested. Although these ORT’s are capable of predicting response to ovarian stimulation, they predict pregnancy outcome poorly. Therefore, the use of ORTs as screening tests to select patients for IVF treatment has been discouraged (Broekmans et al., 2006).

Up to date, the predictive value of ORT’s in most original studies is commonly assessed isolated from other test results or clinical information. Even female age is barely integrated into prediction models. Also, data on the predictive value of ORT’s for pregnancy outcome are often not available (Verhagen et al., 2008).

Meta-analyses using individual patient data may, after addition of patient specific information, like female age, BMI or the etiology of subfertility, as well as the combination of several ORT’s, improve the predictive value of the prediction models (Lee et al., 2009). This might enable the creation of a predictive tool that identifies subgroups of women with specific pregnancy chances, based on their clinical profile.

Conclusion

Systematic reviews and meta-analyses using individual patient data offer a promising, but challenging approach to summarize clinical evidence, thereby facilitating the application of evidence based medicine in reproductive medicine. Compared to conventional systematic reviews and meta-analyses, the value of IPD meta-analysis will depend on the specific research question and on the feasibility of acquiring patient level data for a substantial number of
primary studies. We briefly presented the opportunities of using individual patient data in the context of three ongoing IPD meta-analyses in reproductive medicine. Future results of these studies will show whether our hypothesis, that systematic reviews and meta-analyses with individual patient data contributes to better patient care in reproductive medicine, is true.
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