Evaluating prognosis in unexplained infertility

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Importance: The diagnosis of unexplained infertility presents a dilemma as it signifies both uncertainty about the cause of infertility and the potential for natural conception. Immediate treatment of all would result in overtreatment. Prediction models estimating the likelihood of natural conception and subsequent live birth can guide treatment decisions.
Objective: To evaluate if in couples with unexplained infertility, prediction models are effective in guiding treatment decisions.
Evidence review: This review examines 25 studies that assess prediction models for natural conception in couples with unexplained infertility in terms of derivation, validation, and impact analysis.
Findings: The largest prediction models have been integrated in the synthesis models of Hunault, which includes female age and infertility duration, having been pregnant before and motile sperm percentage. Despite its limited discriminative capacity, this model demonstrates excellent calibration. Importantly, the impact of the Hunault model has been evaluated in randomized clinical trials, and shows that in couples with unexplained infertility and 12-month natural conception chances exceeding 30%, immediate treatment with intrauterine insemination (IUI) and controlled ovarian hyperstimulation is not better than expectant management for 6 months. Below the threshold of 30%, treatment with IUI is superior over expectant management, but immediate in vitro fertilization was not better than IUI.
Conclusion: In couples with unexplained infertility and a good prognosis for natural conception, treatment can be delayed, whereas in couples with a poor prognosis, immediate treatment (with IUI-controlled ovarian hyperstimulation) is warranted.
Relevance: These data indicate that in couples with unexplained infertility, integration of prediction models into clinical decision making can optimize treatment selection and maximize fertility outcomes while limiting unnecessary treatment. (Fertil Steril® 2024;121:717–29. ©2024 by American Society for Reproductive Medicine.)
Key Words: Prognosis, unexplained infertility, prediction model, natural conception

The main ambition of medicine is to improve the health of individuals. To do so, it first needs to be known in which individuals the prognosis for an outcome without intervention is poor or at least mediocre. On the basis of that knowledge, an intervention is then indicated to help an individual in improving that prognosis. For reproductive medicine, the main ambition is to help people who have difficulty getting or staying pregnant. Here, we will discuss prognosis and subsequent prognosis-related treatment of unexplained infertility. Infertility is defined as the absence of conception in couples who have had ≥12 months of unprotected intercourse (1).

UNEXPLAINED INFERTILITY

When couples who want a baby consult a doctor after 12 months of trying in vain, the initial diagnostic work-up will focus on the 3 main components needed for conception: the egg, sperm, and bringing the two together (the tube). The main causes underlying "the egg factor" are anovulation—the oocyte is there but fails to become available for ovulation—or advancing age of the woman, resulting in poor oocyte quality. The "sperm factor" can be related to compromised sperm production or an obstruction in the transport of spermatozoa or its precursor cells, and is initially assessed in a single or repeated semen analysis. The third factor is transport, bringing the egg and spermatozoa together. This can be compromised by sexually transmitted infections, or intra-abdominal pathology including tubal occlusion, endometriosis, or severe adhesions.

Given the above, an initial diagnostic work-up should include an assessment of ovulation and quality of the egg, a semen analysis, and at some stage, a tubal patency test. Normal ovulation can be confirmed by menstrual regularity or urinary luteinizing hormone measurements, ultrasound monitoring, or mid-luteal progesterone measurement, although the latest European Society of Human Reproduction and Embryology

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guideline does not even require evaluation in the presence of regular menstrual cycles (2). Normal semen analysis is confirmed by 1 or 2 semen analyses with normal parameters on sperm's volume, concentration, total count, motility, vitality, and morphology (3).

Tubal patency can be confirmed at hysterosalpingo-contrast-sonography or hysterosalpingogram. Although there is a lack of agreement on whether 1-sided patency is enough to diagnose unexplained infertility, bilateral patency is the most widely adopted criterion (4). A transvaginal sonography should be done to confirm normal cavum uteri and exclude other intra-abdominal pathology, congenital abnormalities, or myometrial abnormalities.

The diagnosis of unexplained infertility requires at least normalcy of the above tests or their equivalents. Of course, this diagnosis is dependent on the number of performed tests. The more tests performed, the less likely a diagnosis of unexplained infertility becomes. If additional tests are abnormal, e.g., a laparoscopy showing adhesions or endometriosis, the infertility is no longer unexplained.

The diagnosis of unexplained infertility brings a dilemma. On the one hand, a couple has experienced the individual disappointment of trying to conceive for 12, 18, or sometimes 24 months without success. This gives from the individual perspective the perception that pregnancy will never happen, especially because other couples in direct proximity conceive quickly. On the other hand, the lack of a clear factor prohibiting conception implies that pregnancy can occur at any moment in these couples. Indeed, in approximately 50% of the couples who tried to conceive in vain for 6 months natural conception occurs in the next 6 months, and in the second year of trying still 50% of couples conceive naturally (5). Although on an individual level, a couple experiences infertility; on a population level, many natural conceptions will occur, indicating that subfertility may be a better term than infertility; albeit that at the moment pregnancy is not achieved, it is impossible to state if this is permanent infertility or, in hindsight, a period of subfertility.

The diagnosis of "unexplained infertility" brings a double message. On one hand, uncertainty about why pregnancy is not happening remains, a treatable cause for infertility has not been found, and a targeted treatment can therefore not be started. On the other hand, the fact that an absolute factor hampering conception has not been identified indicates that natural conception still can occur in any cycle and that the long-term prognosis, without or with treatment is usually good (6, 7). The glass is half full or half empty. Half full: there is nothing abnormal and this is reassuring; half empty: there is no identifiable reason why conception is not occurring and this is frustrating.

A consequence of unexplained infertility is that treatment, when it is started, cannot target a specific cause of infertility. Where ovulation induction overcomes anovulation, or in vitro fertilization (IVF) bypasses tubal occlusion, the treatment of unexplained infertility does not have such an analogy. Treatment in unexplained infertility therefore tries to increase the probability of success by increasing the number of chances per cycle, e.g., by increasing the number of oocytes in intrauterine insemination (IUI) with controlled ovarian hyperstimulation (COH) or by creating multiple embryos in 1 IVF cycle.

PROGNOSIS IN UNEXPLAINED FERTILITY

In deciding when to start treatment for unexplained infertility, prognosis is, or should be, instrumental. Clear causes of infertility, such as anovulation or bilateral tubal blockage, reduce natural fertility chances to almost zero. In unexplained infertility, this is not the case, and it is here where the prognosis for natural conception adds insight.

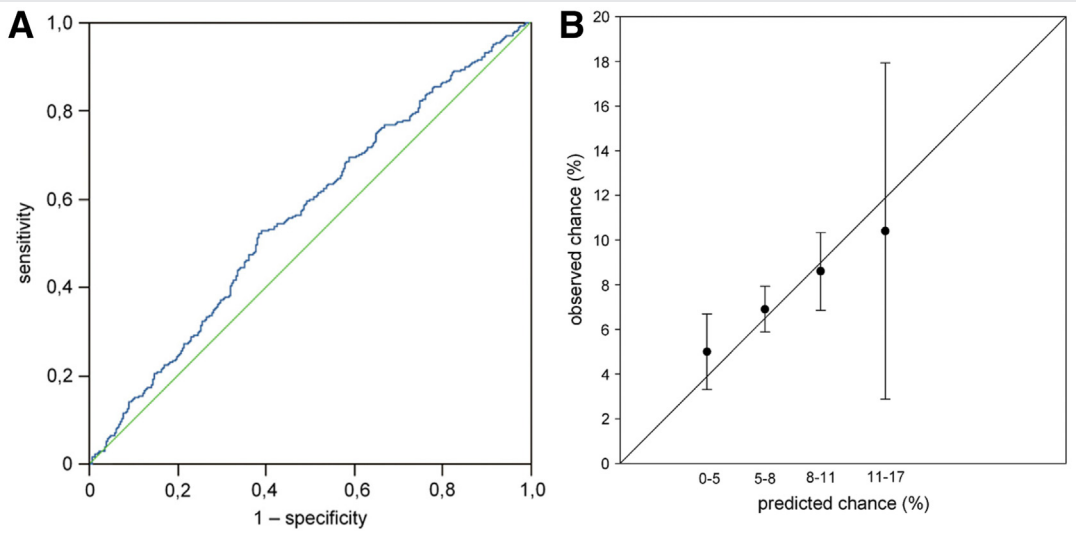
The main prognostic factor for natural fertility is obviously the age of the female partner. Female fertility starts to decline slowly after the age of 30 and decreases, with individual variation, exponentially from approximately 37 years (8). Other factors contributing to this prognosis include duration of infertility, previous conception, semen quality, and body mass index. The best way to integrate these components is in prediction models.

There are 3 phases in the development of prediction models: model derivation, model validation, and impact analysis (9, 10). During model derivation, predictors are identified, on the basis of prior knowledge, and understanding of biological mechanisms, after which it is determined if a predictor independently contributes to prognosis and should be included in the model at what weight, as expressed by a regression coefficient.

In the model validation process, the model's ability to predict outcomes is evaluated. Two fundamental dimensions of predictive performance are discrimination and calibration (11). Discrimination expresses how effectively the model distinguishes between individuals who will and will not experience the event of interest, i.e., conception leading to live birth. In time-to-event scenarios, it assesses the model's capacity to predict whether individuals will experience the event sooner or not at all compared with others. Discriminative capacity is usually expressed as the area under the receiver operating characteristic (ROC) curve, or concordance index (C-index). Calibration refers to the agreement of the model's predictions in aligning with the observed event rates overall. Although discrimination expresses how successful a test can order those with and those without the event, calibration refers to the agreement between the estimated and the observed event rates. Calibration is assessed far less often than discrimination but is in the context of prognosis in unexplained infertility probably more important (12). Various statistical methods can be employed to evaluate these 2 metrics.

Figure 1 demonstrates the assessment of discriminative capacity and calibration for a prediction model for ongoing pregnancy after IUI (13). Figure 1A shows a ROC curve expressing the discriminative capacity of the model. The ROC curve expresses the sensitivity-specificity combinations, with a 100% sensitivity and a 100% specificity expressing perfect accuracy at which all couples achieving pregnancy can be separated from all couples not achieving pregnancy. A perfect sensitivity of 1 at the upper left corner is unattainable in real-world settings; hence, models typically meet expectations when the area under the ROC curve falls between

FIGURE 1



Evaluation of a prognostic model for intrauterine insemination (IUI). (**A**) Discriminative capacity of the model expressed in a receiver operating characteristics (ROC) analysis. The ROC curve demonstrates to what extent the model is able to discriminate between women who achieve ongoing pregnancy and those who do not. The area under the ROC curve was 0.56, indicating poor discriminative capacity. (**B**) Calibration of the model. The calibration plot indicates to what extent the predicted and the observed chance concur. The mean predicted chance is never >1.5% different from the observed probability.

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0.7 and 1. The C-index (area under the ROC curve) of the IUI model of Figure 1A was 0.56, indicating poor discriminative capacity. Figure 1B shows the calibration of the same model. The calibration plot indicates to what extent the predicted and the observed chance concur. Ideally, a perfectly calibrated model would exhibit a diagonal line representing perfect agreement (14). Here, that is not reached, but the mean predicted chance is never >1.5% different from the observed probability, implicating the clinical utility of the model.

Validation can be distinguished in internal and external validation. In internal validation, the model is tested in the group of patients in which it was developed, albeit sometimes with data collected in a separate group of patients evaluated in the same setting. At external validation, the prediction model is evaluated in populations other than the population in which the model was developed.

The third and final phase of model validation consists of impact analysis, which is the evaluation of the implementation of prediction models with documented validity. Impact analysis establishes whether the prediction model enhances physicians' decision making regarding whom to treat, when, and how, ultimately leading to improved patient outcomes (15). This evaluation preferably occurs in the context of a randomized controlled trial (RCT).

OVERVIEW OF EXISTING PREDICTION MODELS FOR NATURAL CONCEPTION

We searched the published literature for studies reporting on models that predicted the occurrence of pregnancy from natural conception, or treatment-free conception. We started from the review of Leushuis et al. (16) and then used the snowballing method to identify articles that cited the models identified. To be selected, studies had to include infertile couples, i.e., couples that were trying to conceive for ≥6–12 months. We found 25 models that were published between 1987 and 2022 (Table 1) (17–41). Among the included studies, there were 15 derivation studies (of which 7 were internally validated), 6 external validation studies, and 4 articles reporting on impact analysis.

DERIVATION STUDIES

The sample size of the derivation models varied between 224 and 5,962. The predominant type of prediction model developed in most studies is Cox regression, taking into account time to pregnancy, and employing either forward or backward stepwise variable selection methods to identify significant predictors. The most frequent predictors were female's age, duration of female infertility, primary or secondary female infertility, and percentage of motile sperm (Table 2 and Supplemental Table 1, available online) (17–41).

Bostofte (17) reported solely on male infertility. Bostofte et al. (18) reported on infertile couples and found that the duration of infertility, female diagnosis and the sperm penetration test predict the time required to conceive. Wichman et al. (19) reported on 900 men suffering infertility with their partners and found that duration of infertility, the age of both partners, a history of male urethritis, male body mass index, and a series of semen characteristics were significant predictors of fertility. Bahamondes et al. (20) found in a case-control study in Argentina among 247 permanent infertile couples

TABLE 1

Characteristics of studies that report on prediction models for treatment-independent pregnancy.

Models	Country	Center	Participants	Exclusion	Sample size	Study design	Endpoints
Model derivation							
Bostofte (17)	Denmark	University hospital	Subfertile men with semen analysis	Exclusion azoospermia	765	Retrospective cohort	Pregnancy
Bostofte et al. (18)	Denmark	University hospital	Subfertile couples	None reported	321	Retrospective cohort	Pregnancy
Wichmann et al. (19)	Finland	Andrological laboratory in university hospital	Subfertile men	Abstinence period <3 d; incomplete sample; azoospermia; donor ins	907	Retrospective cohort	Pregnancy
Bahamondes et al. (20)	Argentina	Fertility clinic	Subfertile couples with 3 y of follow-up	Divorced during study; tubal ligation; recurrent miscarriage; azoospermia	559	Retrospective cohort	Pregnancy
Eimers et al. (22)	The Netherlands	University hospital	Subfertile couples with ovulatory cycle	Azoospermia; normal HSG or laparoscopy	996	Retrospective cohort	Pregnancy
Hunault et al (33)	Canada, the Netherlands	Synthesis of Snick et al. (23), Collins et al. (24), and Eimers et al. (25)	Subfertile couples	Ovulation disorder; tubal pathology; azoospermia	3,920	Prospective cohort	Live birth
Pinborg et al. (26)	Denmark	Four large university hospital	Subfertile couples referred to tertiary clinics	None reported	1,338	Prospective cohort	Live birth
Righarts et al. (29)	New Zealand	Otago Fertility Service	Subfertile couples	None reported	1,386	Prospective cohort	Live birth
Model derivation with internal validation							
Collins et al. (21)	Canada	11 academic infertility clinics	Subfertile couples visiting infertility clinic for the first time	None reported	2,198	Prospective cohort	Live birth
Snick et al. (23)	The Netherlands	Nonacademic hospital	Subfertile couples from a secondary care fertility center	None reported	726	Prospective cohort	Live birth
Eijkemans et al. (25)	The Netherlands	32 IVF clinics	Couples scheduled for IVF	None reported	5,962	Prospective cohort	Ongoing pregnancy
Jedrzejczak et al. (30)	Poland	University hospital	Subfertile men matched with healthy fertile sperm donors	No motile sperm	224	Prospective cohort	Pregnancy
Bensdorp et al. (28)	The Netherlands	38 fertility centers	Subfertile couples with unexplained/mild male subfertility	Bilateral tubal pathology; TMC $<1 \times 10^6$; tertiary referrals	5,184	Prospective cohort	Ongoing pregnancy
van Eekelen et al. (31)	The Netherlands	38 fertility centers	Subfertile couples with unexplained/mild male subfertility	Bilateral tubal occlusion; anovulation; TMC $<1 \times 10^6$	4,999	Prospective cohort	Ongoing pregnancy
McLernon et al. (32)	Scotland, UK	university hospital	Subfertile couples with unexplained/mild male subfertility	Bilateral tubal pathology; TMC $<1 \times 10^6$; tertiary referrals	1,316 d 5,184 v	Prospective cohort	Live birth
External model validation							
Hunault et al. (24)	Canada	See Collins 1995	Subfertile couples at a university clinic	Uni/bilateral tubal disease; azoospermia; anovulation	1,061	Prospective cohort	Live birth

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TABLE 1

Continued.

Models	Country	Center	Participants	Exclusion	Sample size	Study design	Endpoints
Hunault et al. (34)	The Netherlands	2 university hospitals	Subfertile couples in with mild male, cervical or unexplained subfertility External validation of Hunault 2004	Uni/bilateral tubal pathology; azoospermia; ovulation disorder	302	Prospective cohort	Live birth
van der Steeg et al. (27)	The Netherlands	38 fertility centers	Subfertile couples with unexplained/mild male subfertility	Bilateral tubal pathology; TMC $<1 \times 10^6$ tertiary referrals	3,021	Prospective cohort	Ongoing pregnancy
Farquhar et al. (36)	New Zealand	Single fertility clinic	Subfertile couples referred by primary care with unexplained subfertility	Bilateral tubal pathology; TMC $<1 \times 10^6$	249	Prospective cohort	Live birth
van Eekelen et al. (35)	The Netherlands	38 fertility centers	Subfertile couples with unexplained infertility	Anovulation; uni/bilateral tubal occlusion; poor semen quality, endometriosis	1,203	Retrospective cohort	Ongoing pregnancy
Song et al. (37)	Australia	Single fertility clinic	Subfertile couples seeking fertility consultation for the first time	Donor; genetic disorders; recurrent miscarriage	496	Retrospective cohort	Live birth
Impact studies							
Steures et al. (38)	The Netherlands	38 fertility centers	Couples with unexplained/ mild male subfertility ; Hunault prognosis 30%–40%	Bilateral tubal pathology; TMC $<1 \times 10^6$ tertiary referrals	253	RCT	Ongoing pregnancy
Farquhar et al. (39)	New Zealand	2 fertility clinics	Couples with unexplained/ mild male subfertility ; Hunault prognosis <30%	Female age >42; anovulation; donor; BMI>35 endometriosis	201	RCT	Live birth
Wessel et al. (40)	The Netherlands	17 fertility centers	Couples with unexplained/ mild male subfertility ; Hunault prognosis <30%	Previous fertility treatment; anovulation; donor sperm	178	RCT	Ongoing pregnancy
Bensdorp et al. (41)	The Netherlands	38 fertility centers	Couples with unexplained/ mild male subfertility ; Hunault prognosis <30%	Bilateral tubal pathology; anovulation; TMC $<1 \times 10^6$	602	RCT	Live birth

Note: The table describes 25 models included in this review article, detailing their main characteristics such as the study location, participant inclusion and exclusion criteria, sample size, and study design. These models were published between 1987 and 2022. Among the studies included, there were 15 derivation studies (7 of which also conducted internal validation), 6 validation studies, and 4 articles reporting on impact analysis.
d = derivation; IVF = in vitro fertilization; TMC = total motile count; v = validation.

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TABLE 2

Common predictors in prediction models for treatment-independent pregnancy across included studies.

Model	Age of female	Age of male partner	Duration of infertility/ subfertility	Previous pregnancy (primary or secondary)	Detailed pregnancy history	Female Body mass index	Motile sperm concentration	Quality of sperm motility	Sperm morphology	Result of Postcoital Test (PCT)	Gynecological disease	Male reproductive defect	Female reproductive defect	Referral status
Derivations studies														
Bostofte (17)		✓					✓		✓					
Bostofte et al. (18)			✓										✓	
Wichmann et al. (19)	✓		✓			✓	✓	✓	✓			✓		
Bahamondes et al. (20)	✓		✓	✓					✓					
Eimers et al. (22)	✓		✓	✓			✓			✓				
Collins et al. (21)	✓		✓	✓	✓						✓	✓		
Snick et al. (23)			✓							✓			✓	
Hunault et al. (33)	✓		✓	✓			✓							✓
Eijkemans et al. (25)	✓		✓									✓	✓	
Pinborg et al. (26)	✓		✓											
Bensdorp et al. (28)	✓		✓	✓	✓	✓		✓	✓		✓			✓
Righarts et al. (29)	✓		✓	✓		✓							✓	
Jedrzejczak et al. (30)							✓	✓	✓			✓		
van Eekelen et al. (31)	✓		✓	✓				✓						✓
McLernon et al. (32)	✓		✓	✓	✓									
Validation studies														
Hunault et al. (24)	✓		✓	✓			✓							✓
Hunault et al. (34)	✓		✓	✓			✓			✓				✓
van der Steeg et al. (27)	✓		✓	✓						✓				✓
Farquhar et al. (36)	✓		✓	✓			✓							✓
van Eekelen et al. (35)	✓		✓	✓										✓
Song et al. (37)	✓		✓	✓										✓
Impact studies														
Steures et al. (38)	✓		✓	✓			✓							✓
Bensdorp et al. (41)	✓		✓	✓			✓							✓
Farquhar et al. (39)	✓		✓	✓			✓							✓
Wessel et al. (40)	✓		✓	✓			✓							✓

Note: The table summarizes the most common predictors in the prediction models across 25 studies. Female age, duration of subfertility, sperm motility, type of subfertility, and referral source are the most frequently observed predictors. Some variables have been grouped for clarity, such as "sperm morphology" encompassing "number of morphologically normal spermatozoa (%)." Similarly, "motile sperm density" and "number of motile spermatozoa (%)" are combined as "motile sperm concentration." "Female reproductive defect" represents issues such as tubal and ovulation disorders. "Detailed pregnancy history" includes prior intrauterine pregnancies within the current relationship, whether achieved through natural conception or fertility treatment, resulting in ongoing pregnancy or miscarriage. Rare predictors are excluded from the table.

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and 312 couples that fell pregnant after a period of infertility that sperm morphology, the woman's age, type and duration of infertility, her history of pelvic surgery, and duration of menstrual cycles were predictors of pregnancy. None of these early studies provided a formal prediction model for the couple.

Collins et al. (21), Eimers et al. (22), and Snick et al. (23) performed large-scale cohort studies with sample sizes of 2,198, 996, and 726, which were focused on the couples and not on the male partner alone. Female age, duration of infertility and pregnancy history (having been pregnant before or not) were found to be the most consistent predictors. The prediction scores developed by Collins et al. (21) and Snick et al. (23) are deemed to have 62% and approximately 76%–79% accuracies, respectively, assessed via ROC analysis. However, calibration assessment was lacking for both studies. Eimers model demonstrated strong calibration under the split-half validation method, predicted pregnancies were in close agreement with observed pregnancies. Hunault et al. (24) then integrated Collins et al. (21), Eimers et al. (22), and Snick et al. (23) into a new synthesis model.

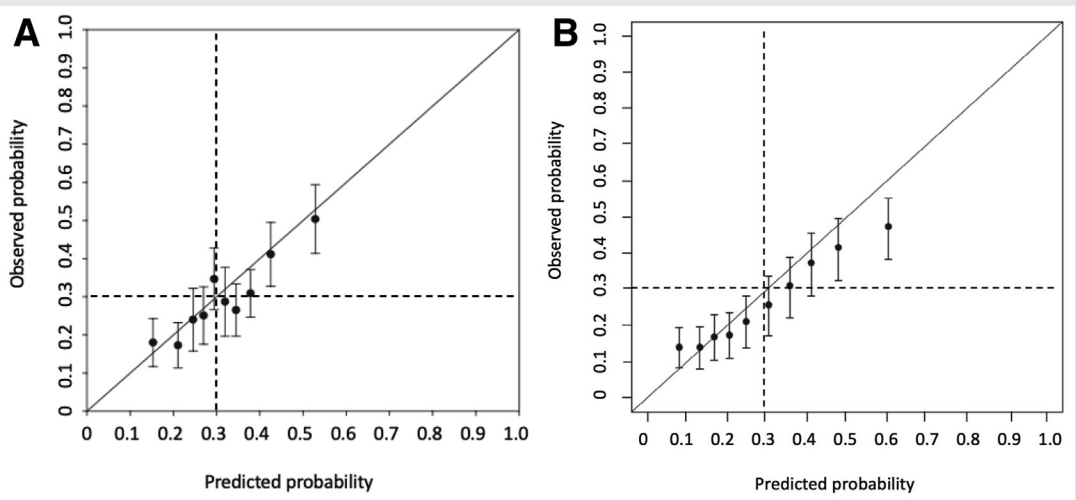
Eijkemans et al. (25) conducted a cohort study in the Netherlands studying treatment-free ongoing pregnancy among 5,962 couples on the waiting list for IVF/intracytoplasmic sperm injection treatment. They found female age, duration of infertility, previous pregnancies, and diagnostic category to be predictive. This study reported on couples scheduled for IVF with a duration of infertility of >3 years. The absolute treatment-free pregnancy chances were approximately 10%, resulting in low calibration when the model would be applied in couples first consulting a specialist. This model demonstrated a discriminative index (C-index) of 0.65 after correcting for optimism, indicating a 65% ability to distinguish high-chance from low-chance couples.

Pinborg et al. (26) reported on 1,338 infertile couples referred to tertiary clinics. The model including female age, duration of infertility, and previous treatment cycles as well as the diagnostic category reported on the overall chance of success, including pregnancies achieved after treatment. Natural conception contributed to 20% of all live births.

Bensdorp et al. (28) extended the Hunault model to predict the likelihood of natural conception resulting in an ongoing pregnancy among >5,000 subfertile couples with unexplained or mild male subfertility collected by van der Steeg et al. (27) for their validation study (see below). The revised model incorporated all predictors from the original Hunault model and an additional 7 variables: woman's body mass index, cycle length, basal follicle-stimulating hormone levels, tubal status, history of previous pregnancies in the current relationship (ongoing pregnancies after natural conception, fertility treatment, or miscarriages), semen volume, and semen morphology. The revised model showed improved discrimination (C-index: 0.71) compared with the Hunault model (C-index: 0.59). Calibration analysis also revealed better agreement with observed pregnancy rates for the revised model, leading to reclassification in 39% of couples, indicating enhanced prediction accuracy (Fig. 2) (28).

Righarts et al. (29) assessed the likelihood of live birth in 1,386 infertile couples in a prospective cohort study among couples visiting a single infertility clinic in New Zealand. Significant predictors included female age, duration of infertility, female body mass index, type of infertility (primary/secondary), socioeconomic status, and assisted reproductive

FIGURE 2



Calibration of prognostic models for natural conception leading to live birth. (**A**) The calibration of the synthesis model according to Hunault as evaluated by van der Steeg (13). (**B**) The calibration for the revised model according to Bensdorp et al. (14). In both figures, the dashed line marks the predicted and observed 30% 12-mo conception rate leading to live birth rate. Both models identify approximately 50% of the couples in whom chances of natural conception are above 30%.

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technology diagnostic category (29). Importantly, this model included pregnancies conceived with treatment.

Jedrzejczak et al. (30) studied 109 men from infertile couples without female infertility factor and 113 healthy fertile sperm donors, and found that 12 parameters comprising broadly 4 semen measurements—sperm concentration, total progressive motility, normal morphology, and the hypo-osmotic swelling test—yielded a satisfactory prediction of spontaneous conception. This prediction model achieved 90.3% accuracy in predicting conception and 90.8% accuracy in predicting its absence (30).

van Eekelen et al. (31) used, just like Bensdorp et al. (28), the cohort collected by van der Steeg et al. (27) to develop a so-called dynamic prediction model (31). Although the relevant predictors stayed the same, the revised model showed better calibration and stable discriminative ability over time. The revised model outperformed the Hunault model with a higher C-index (0.71 vs. 0.59), resulting in improved agreement between predicted and observed pregnancy rates and allowing to reassess the prognosis after a couple has waited with treatment for 6 months, thus personalizing prediction. McLernon et al. (32) also developed a dynamic prediction model. The novelty of this model was that it estimated the chances of conception after expectant management and different fertility treatments over time in couples with unexplained subfertility. The dynamic prediction model showed moderate discriminatory ability (concordance 0.60–0.71) over various prediction months. Calibration analysis indicated good alignment between predicted and observed conception rates, with minor evidence of overestimation at some time points and minimal overfitting.

As described above, many of the model derivation studies mentioned above also incorporated internal validation in their analysis. Collins et al. (21), Snick et al. (23), Bensdorp et al. (28), Jedrzejczak et al. (30), van Eekelen et al. (31), and McLernon et al. (32) assessed discriminative capacity in ROC analysis, and reported a C-index as high as 0.71. Bensdorp et al. (28), van Eekelen et al. (31), and McLernon et al. (32) also assessed calibration and reported it to be acceptable.

Table 2 (17–41) provides an overview of the common predictors within prediction models for treatment-independent pregnancy across the 25 included studies. Female age, duration of subfertility, sperm motility, type of subfertility, and referral source have been found to be the most frequent predictors. Notably, rare predictors are omitted from the table for conciseness and relevance.

EXTERNAL VALIDATION STUDIES

We identified 6 studies that specifically performed external validation (Table 1) (17–41). These studies were performed in Canada, the Netherlands, New Zealand, and Australia, with sample sizes varying between 249 and 3,021. Hunault et al. (24) performed a validation from the Eimers model from 1994, and assessed on a Canadian population of 1,061 subfertile couples planning for IVF with a diagnosis of cervical hostility, male subfertility, or unexplained subfertility, and validated the Eimers model which included female age, duration of subfertility, type of female subfertility, and sperm motility as predictors, finding a C-index of 0.62 and a good calibration between the prognostic index and conception within 1 year resulting in live birth.

The most important model is probably the synthesis model of Hunault, on the basis of almost 4,000 couples (33). This model was externally validated in a Dutch study with 300 couples in Dutch University hospitals, and then in a large nationwide study in the Netherlands in over 30 hospitals involving >3,000 couples (27, 34). The C-index of this model was 0.65 in the Hunault validation and 0.59 in the van der Steeg validation. Much more importantly, the calibration of the model was excellent, with just over 30% of the couples having an expected successful conception rate between 30% and 40%, and 20% of the couples having an expected conception rate above 40% (Fig. 2).

van Eekelen et al. (35) validated a dynamic model developed in 2017 using data from 1,203 couples with unexplained subfertility. The model included predictors like female age, duration of subfertility, sperm motility, type of subfertility, and referral source to the fertility clinic. Calibration plots showed good agreement between predicted and observed pregnancy rates, while discrimination was moderate, as measured by C-index ranging from 0.60 to 0.64, consistent with internal validation.

Farquhar et al. (36) conducted a validation of the Clinical Priority Access Criteria score in New Zealand, comparing it with the Hunault prediction model. A total of 249 subfertile couples with unexplained infertility who were referred by primary care were assessed for live birth rate. Both scores had a C-index of 0.63, but the Hunault model showed better calibration. The Clinical Priority Access Criteria score correlated reasonably well with the Hunault prediction score, although the latter recommended assisted reproductive technology for 26% more couples. Although both scores had similar discriminative capacities, the Hunault prediction model exhibited superior calibration (36).

Song et al. (37) used an adapted model on the basis of the Hunault model to predict natural conception in 496 subfertile couples seeking fertility consultation for the first time (27, 42). About half of the couples with unexplained or mild male infertility, and 65% of the couples had an intermediate or even good prognosis for natural conception. This demonstrates that a prognostic model could predict a couple's chances of natural conception and the benefit they derive from treatment.

IMPACT STUDIES

We identified 4 impact studies that used prediction models. These studies used prognosis for natural conception, more specifically the Hunault model, as an entry criterion for their study. Three studies randomized couples with unexplained or mild male infertility to IUI-COH or expectant management, whereas the fourth study compared IVF and IUI.

Steures et al. (38) randomized 253 couples with unexplained infertility with a moderate (30%–40%) chance of natural conception within 12 months to IUI-COH or expectant management for 6 months. The primary endpoint was

ongoing pregnancy. Cumulative ongoing pregnancy rates after 6 months were approximately 25% in both strategies. At 3-year follow-up, cumulative live birth rates after IUI-COH followed by IVF were almost 75%, independent of whether the treatment with IUI-COH (followed by IVF) had started immediately or after 6 months (6, 38). The investigators concluded that in couples facing unexplained subfertility and having an intermediate prognosis (30%–40%), there appears to be no substantial benefit from an immediate start with IUI-COH.

Farquhar et al. (39) and Wessel et al. (40) performed randomized studies also evaluating IUI-COH vs. expectant management in couples with unexplained infertility, but their studies were limited to couples with a poor prognosis, defined as <30% natural conception chances in 12 months. Primary outcomes were cumulative live birth rate and ongoing pregnancy leading to a live birth, respectively. In contrast with Steures et al. (38), IUI-COH resulted in both studies in significantly higher ongoing pregnancy rates. Although 6-month cumulative live birth rates after IUI-COH were 31% and 33%, comparable with Steures et al. (38), these rates were 9% and 13% considerably lower for expectant management (39, 40).

The findings in these 3 studies confirm the impact that prediction models can have on fertility management. Although couples with unexplained infertility from a diagnostic point of view are a homogeneous group, the prognostic assessment with the Hunault model allows a different approach to couples that benefit from immediate treatment with IUI-COH and couples in whom a period of expectant management still results in acceptable pregnancy rates. Of course, the exact moment of the start of treatment is subject to the individual preferences of a couple. Although some couples want to start treatment as soon as possible, other couples might prefer a delay in medical treatment.

Bensdorp et al. (41) randomized 602 couples, where the female partners had an unfavorable prognosis (<30%) for natural conception and a diagnosis of unexplained or mild subfertility for the male partners, to 1 of 3 groups: in vitro fertilization with single embryo transfer, in vitro fertilization in a modified natural cycle, or IUI-COH. The primary outcome was natural conception leading to an ongoing pregnancy. This RCT indicated no benefit from the immediate start of IVF over IUI-COH in couples with a poor prognosis, with 12-month cumulative ongoing pregnancy rates after IVF and after IUI-COH.

These 4 high-quality RCTs all incorporated the prognosis for natural conception as an inclusion criterion and therefore should be instrumental in informing guidelines. To summarize, Steures et al. (38) indicate that in couples with a moderate to good prognosis for natural conception (>30% in 12 months), treatment with IUI-COH offers no additional benefit over expectant management. Conversely, in couples with a poor prognosis for natural conception (<30% in 12 months), IUI-COH proves to be superior to expectant management, as shown in the studies by Wessel et al. (40) and Farquhar et al. (39). Furthermore, as a first-line treatment option, IUI-COH is found to be equally effective as IVF, as indicated by Bensdorp et al. (41).

DISCUSSION

In diagnostic terms, unexplained and mild male infertility is a homogenous group, defined by the absence of absolute factors that prevent conception, and, with increasing female age, reaching into diminished ovarian reserve. Prediction models can help to classify these couples. In this review, we have shown that these models, and in particular the synthesis model of Hunault et al. (33), are reliable in distinguishing couples with unexplained infertility with a good prognosis for natural conception that justifies expectant management from couples where prognosis is poor, and therefore treatment can be offered.

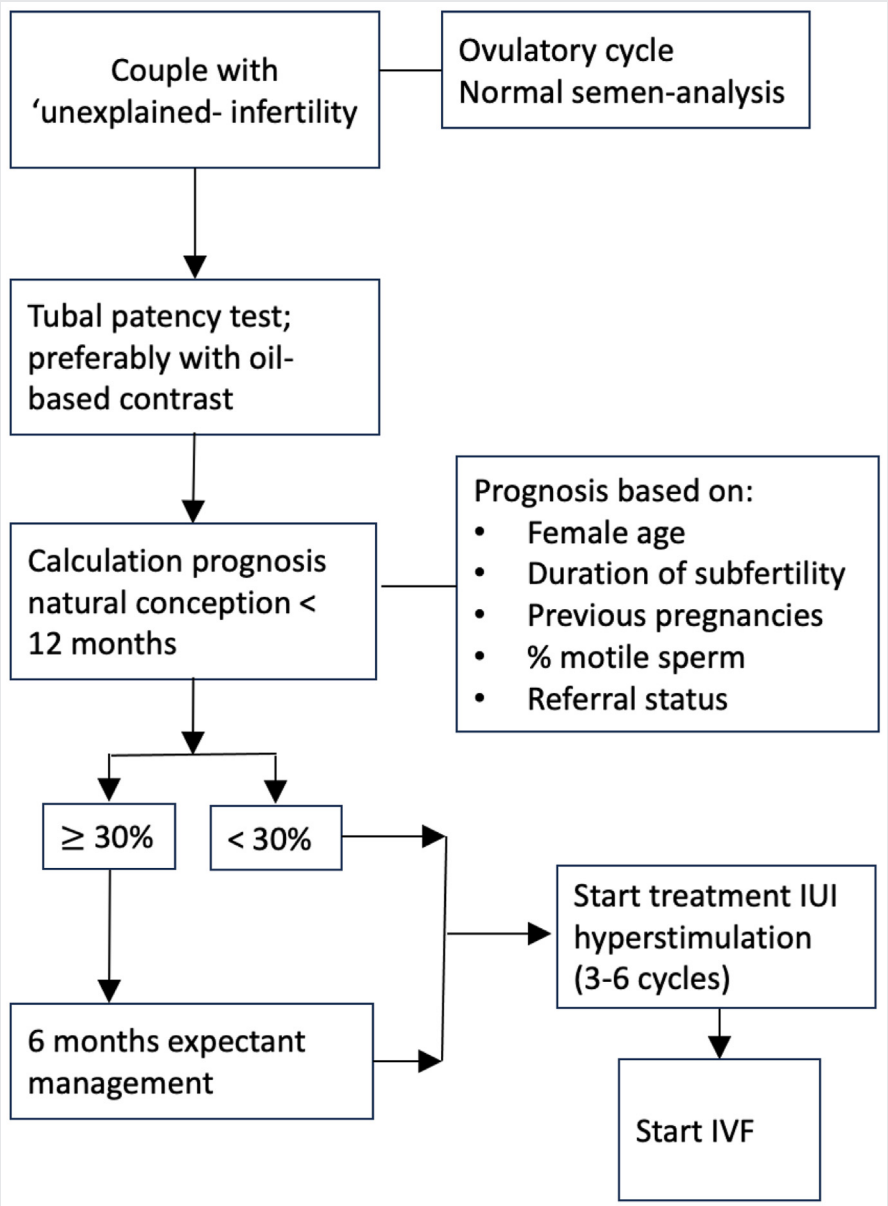
In a review in 2011, we mentioned several challenges in assessing prediction models in reproductive medicine (16). First, there is debate about performance measures to use for prediction models and how to interpret them. Traditionally, the area under the ROC curve or C-index is used as a measure for discriminative capacity. We found the discriminative capacity of the prediction models for natural conception to be mediocre, with a C-index mostly between 0.60 and 0.70. This is caused by the fact that conception cannot be predicted with 100% certainty, with highest prediction rates of approximately 50%–60%. The fact that being in the high prognostic category does not guarantee success maximizes the C-index, but that calibration still can be good is demonstrated—albeit for IUI—in Figure 1 (6). Indeed, we render the calibration of the Hunault synthesis model sufficient for clinical practice.

Second, there is concern about the lack of validation of prognostic models, in particular external validation. Good performance at external validation is a minimal requirement to be eligible for use in clinical practice. We found 6 external validation studies performed in the Netherlands, Canada, New Zealand, and Australia, all reporting adequate discrimination and calibration (24, 27, 34–37). More importantly, we identified a series of impact studies in which the Hunault prediction model for natural conception is used to guide recruitment for RCTs. This allows evaluation of the impact of this model on clinical practice.

Figure 3 provides a flowchart that can be used for the management of couples with unexplained infertility. After confirmation of ovulation, and exclusion of severe male factor and tubal pathology, a prognosis for natural conception (Hunault synthesis model) should guide decision making. If the probability of treatment-independent conception within 12 months is >30 %, 6 months of expectant management should be offered. For couples with a prognosis <30%, or infertile couples who have tried natural conception for an additional 6 months, treatment with IUI-COH followed by IVF can be offered.

We limited this review to prediction models for natural conception. Obviously, the management of couples with unexplained infertility can also be guided by the prediction of pregnancy after IUI or IVF. It should be noted that many of the predictors for natural conception have a similar impact

FIGURE 3



Proposed flowchart for the management of couples with unexplained infertility. After confirmation of ovulation, and exclusion of severe male factor and tubal pathology, a prognosis for natural conception (Hunault synthesis model) should guide decision making. If the probability of treatment-independent conception within 12 mo is >30%, 6 mo expectant management should be offered. For couples with a prognosis <30%, or infertile couples who have tried natural conception for an additional 6 mo, treatment of intrauterine insemination with ovarian hyperstimulation (IUI-COH) followed by in vitro fertilization (IVF) can be offered.

Au. Prognosis in unexplained infertility. Fertil Steril 2024.

on the outcome of IUI or IVF (Table 2) (17–41). Older female age will negatively impact conception chances in all 3 strategies, thus making it less useful as a treatment-selection marker. Most impact is to be expected from predictors that have a negative impact on natural conception, although they do not or only marginally affect the success changes after IUI or IVF. One example is severe tubal pathology, which will reduce natural fertility chances or IUI-success to close to zero, whereas it hardly reduces success chances after IVF. Such treatment-selection markers, however, are rare. To optimize the knowledge on treatment-selection markers, we recommend routine measurement of potential predictors as baseline characteristics in RCTs.

The dynamic prediction model by van Eekelen et al. (31) was developed to make predictions repeatedly over any chosen time of expectant management. Although it aims to provide treatment tailored to couples' situations, its usefulness for counseling is limited. The dynamic prediction model

leaves couples in an uncertain limbo in deciding how long they need to wait until receiving treatment, whereas the Hunault model assists in a binary decision between starting treatment immediately or 6 months later. For couples with unexplained infertility who tried to conceive for 6 or more months in vain and frustratingly found no identifiable causes, the Hunault model gives a straightforward answer, thus adding clarity and simplifying patients' decision making.

At the moment, most systematic reviews evaluating treatment do not take into account prognostic aspects. Ayeleke et al. (43) reviewed 15 trials involving 2,068 couples with unexplained infertility to compare IUI with timed intercourse or expectant management for unexplained subfertility. No significant difference in live birth rates was found between the groups across all cycles. However, the investigators concluded that treatment with IUI-COH probably results in higher cumulative live birth rates compared with expectant management in couples with a low prediction score of natural conception. Future reviews should incorporate prognostic factors, which is possible if the reviews are on the basis of individual participant data. Lai et al. (44) recently performed such a review comparing IUI-COH vs. IVF, but this still has to be done for the comparison IUI vs. no treatment.

One important clinical characteristic of "unexplained infertility" is that conception still can occur naturally. As such, it is important to realize that in the definition of other categories of infertility, such as male infertility or diminished ovarian reserve, there is no absolute threshold between these diseases and unexplained infertility. Because it is known that natural conception occurs quite frequently in couples with (mild) male infertility, the strictness of the World Health Organization criteria can be questioned (45). The same is true for diminished ovarian reserve, where biology follows a gradual scale rather than an arbitrary cut-off (46). For clinical practice, definitions should be based on predictive factors, or even better, established treatment effects, rather than on the opinion of experts at consensus meetings.

It is likely some couples currently "diagnosed" with unexplained infertility have an underlying cause of their infertility, but the current stage of clinical practice and its underlying science does not allow detection of these causes. Examples include altered uterine contractility, which is likely to play a role in IVF success, and therefore might also be a cause in couples currently labeled with unexplained infertility (47). Dislodging of debris in tubes can occur through tubal flushing, thus restoring normal fertility (48). In vitro fertilization might overcome some of these unknown causes of unexplained infertility, simply by bypassing a substantial part of the normal route to conception.

Even though embryos are created, meaning eggs and sperm are normal and fallopian tubes are patent, a lot of couples still cannot get pregnant because of implantation failure. Although there is no reliable test so far to prove whether and how the implantation process was compromised, there is a growing body of research in this regard (49–51). Possibly, knowledge on the cause of implantation failure and tailored treatment to overcome it will alter clinical management of couples currently labeled with unexplained infertility.

For unexplained infertility and its neighboring diseases, a probabilistic approach, as was applied in prenatal screening for Down's syndrome, before the introduction of the almost 100% accurate non-invasive-prenatal-testing, might be preferable. Randomized controlled trials should then determine the threshold where treatment benefit starts, like the 30% cut-off for natural conception in unexplained infertility (38–40).

Meanwhile, a period of expectant management does not mean that nothing can be done. A 6-months window without treatment means that attention can be paid to optimize lifestyle and prepare for pregnancy, if that has not been done yet. In addition, other fertility promoting treatments, including tubal flushing with oil-based contrast can be offered in this window (52, 53).

In conclusion, unexplained infertility is a 2-faced condition. Although no treatable cause of infertility is found, conception prospects both natural as well as after treatment are good. Prediction models can help identify couples that benefit from immediate treatment and couples in whom treatment might be delayed for $\leq$6 months as treatment is not adding to the natural prospects.

CRediT Authorship Contribution Statement

Ling Shan Au: Data curation, Formal analysis, Investigation, Validation, Software, Visualization, Writing – original draft, Writing – review & editing. **Qian Feng:** Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Laxmi Shingshetty:** Writing – original draft, Writing – review & editing. **Abha Maheshwari:** Conceptualization, Writing – original draft, Writing – review & editing. **Ben W. Mol:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Resources, Validation, Writing – original draft, Writing – review & editing.

Declaration of Interests

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