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ORIGINAL ARTICLE *Infertility*

Age-related natural fertility outcomes in women over 35 years: a systematic review and individual participant data meta-analysis

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STUDY QUESTION: What is the rate of natural conception leading to ongoing pregnancy or livebirth over 6–12 months for infertile women of age ≥35 years?

SUMMARY ANSWER: Natural conception rates were still clinically relevant in women aged 35 years and above and were significantly higher in women with unexplained infertility compared to those with other diagnoses.

WHAT IS KNOWN ALREADY: In recent years, increasing numbers of women have attempted to conceive at a later age, resulting in a commensurate increase in the need for ART. However, there is a lack of data on natural fertility outcomes (i.e. no interventions) in women with increasing age.

STUDY DESIGN, SIZE, DURATION: A systematic review with individual participant data (IPD) meta-analysis was carried out. PubMed, MEDLINE, EMBASE, the Cochrane Library, clinicaltrials.gov were searched until 1 July 2018 including search terms 'fertility service', 'waiting list', 'treatment-independent' and 'spontaneous conception'. Language restrictions were not imposed.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Inclusion criteria were studies (at least partly) reporting on infertile couples with female partner of age ≥35 years who attended fertility services, underwent fertility workup (e.g. history, semen analysis, tubal status and ovulation status) and were exposed to natural conception (e.g. independent of treatment such as IVF, ovulation induction and tubal surgery). Studies that exclusively studied only one infertility diagnosis, without including other women presenting to infertility services for other causes of infertility, were excluded. For studies that met the inclusion criteria, study authors were contacted to provide IPD, after which fertility outcomes for women of age ≥35 years were retrieved. Time to pregnancy or livebirth and the effect of increasing age on fertility outcomes after adjustment for other prognostic factors were analysed. Quality of studies was graded with the Newcastle–Ottawa Scale (non-randomised controlled trials (RCTs)) or the Cochrane Risk of Bias tool (for RCTs).

MAIN RESULTS AND THE ROLE OF CHANCE: We included nine studies (seven cohort studies and two RCTs) ($n = 4379$ women of at least age 35 years), with the observed composite primary outcome of ongoing pregnancy or livebirth occurring in 429 women (9.8%) over a median follow-up of 5 months (25th to 75th percentile: 2.5–8.5 months). Studies were of moderate to high quality. The probability of natural conception significantly decreased with any diagnosis of infertility, when compared with unexplained infertility. We found non-linear effects of female age and duration of infertility on ongoing pregnancy and tabulated the predicted probabilities for unexplained infertile women aged 35–42 years with either primary or secondary infertility and with a duration of infertility from 1 to 6 years. For a 35-year-old woman with 2 years of primary unexplained infertility, the predicted probability of natural conception leading to ongoing pregnancy or livebirth was 0.15 (95% CI 0.11–0.19) after 6 months and 0.24 (95% CI 0.17–0.30) after 12 months. For a 42-year-old woman, this decreased to 0.08 (95% CI 0.04–0.11) after 6 months and 0.13 (95% CI 0.07–0.18) after 12 months.

LIMITATIONS, REASONS FOR CAUTION: In the studies selected, there were different study designs, recruitment strategies in different centres, protocols and countries and different methods of assessment of infertility. Data were limited for women above the age of 40 years.

WIDER IMPLICATIONS OF THE FINDINGS: Women attending fertility services should be encouraged to pursue natural conception while waiting for treatment to commence and after treatment if it is unsuccessful. Our results may aid in counselling women, and, in particular, for those with unexplained infertility.

STUDY FUNDING/COMPETING INTEREST(S): S.J.C. received funding from the University of Adelaide Summer Research Scholarship. B.W.M. is supported by a NHMRC Investigator grant (GNT1176437), B.W.M. reports consultancy for ObsEva, Merck, Merck KGaA, iGenomix and Guerbet. B.W.M. reports research support by Merck and Guerbet.

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Key words: infertility / IVF / ART / waiting lists / time factors / maternal age / time-to-pregnancy / middle-age / aging

Introduction

Sharp declines in fertility occur with increasing female age. These dramatic changes are generally in conjunction with a decreasing ovarian reserve. The mechanisms behind this deterioration in follicle number and quality, and menstrual cycle changes have yet to be precisely elucidated (Broekmans *et al.*, 2009). In addition, there appears to be considerable natural variation in this decline in fertility, which has been shown to start at different female ages (De Brucker *et al.*, 2013).

Current trends in high-income societies indicate a postponement of childbearing in association with accessibility to contraception, economic prosperity, increased education and participation of women in the workforce (Leridon, 2006; Max Planck Institute for Demographic Research (Germany) and Vienna Institute of Demography (Austria), 2019). Such delays in childbearing naturally result in a heightened average age of first attempt at conception, a proportional increase in women above the age of 30 years having their first child and higher failure rates of natural conception (Lutz *et al.*, 2003). The follow-through effect can be observed in the disproportionate use of fertility services among older women (Adamson *et al.*, 2018; Centers for Disease Control and Prevention ASfRM and Society for Assisted Reproductive Technology, 2018; Fitzgerald *et al.*, 2019).

Along a similar vein, since the first successful IVF cycle for tubal infertility in 1978, indications for treatment have expanded to include women of advanced age with unexplained infertility (Steptoe and Edwards, 1978; Adamson *et al.*, 2018; Centers for Disease Control and Prevention ASfRM and Society for Assisted Reproductive Technology, 2018; Fitzgerald *et al.*, 2019). Controversies arise in the management of these women as IVF success rates are age-dependent, and the rate of maternal and foetal adverse events also escalates with increasing age (Adamson *et al.*, 2018; Centers for Disease Control and Prevention ASfRM and Society for Assisted Reproductive Technology, 2018; Fitzgerald *et al.*, 2019). However, given the accelerated decline in fecundity in women over the age of 30 years, delaying ART in favour of pursuing natural conception may result in time-sensitive irreversible losses of ovarian reserve, which further jeopardises fertility outcomes (Habbema *et al.*, 2015). This is the dilemma of female age in managing infertile couples (Eshre Capri Workshop Group, 2017).

Data on natural fertility outcomes (i.e. no interventions) with increasing age are required in order to empower women to make informed choices when deciding on fertility treatments. The only available data at present are derived from historical non-contraceptive natural fertility studies from the late 20th century and it is unknown whether such fertility outcomes are applicable to women of the 21st century (Henry, 1965; Leridon, 1977; Eijkemans *et al.*, 2014). Individual participant data (IPD) meta-analysis is a powerful modern tool allowing for the extraction, combination and analysis of data from clinical studies. Such an approach is suited to investigating natural fertility outcomes for women of older reproductive age since individual study datasets are generally too small to make accurate predictions for this subgroup of women.

We aimed to answer the following questions using IPD meta-analysis:

- What is the rate of natural conception leading to livebirth over 6–12 months for infertile women of age ≥35 years?
- What are the factors affecting time to conception leading to livebirth?

Materials and methods

Criteria for considering studies in this review

Participants.

IPD of studies reporting (fully or partially) on women aged ≥35 years attending fertility services. Subfertility was defined as 'a disease characterised by the failure to establish a clinical pregnancy after 12 months

of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner' (Zegers-Hochschild *et al.*, 2017).

Types of studies.

The following study designs were eligible: case-control studies, cohort studies (prospective and retrospective) and randomised controlled trials (RCTs).

Interventions.

Studies reporting on fertility outcomes independent of ART (e.g. IVF, surgery, tubal catheterisation or ovulation induction) were included. These included women undergoing a diagnostic fertility work-up, women on a waiting list for treatment or women who discontinued treatment. Studies on women undergoing non-artificial interventions (e.g. timed intercourse, lifestyle advice) were also eligible. Studies only reporting on fertility outcomes dependent on ART were excluded. Studies on women that have undergone interventions that have permanently altered their reproductive system (e.g. tubal surgery) were also excluded.

Outcome measures.

The primary outcome measure was a composite of the cumulative rate of natural conceptions leading to ongoing pregnancy and the cumulative rate of natural conceptions leading to livebirth. This is because livebirth was not recorded for all women in all cohorts and, in absence, ongoing pregnancy was used. We refer to this composite outcome as (natural conception leading to) ongoing pregnancy.

Time to natural conception leading to ongoing pregnancy or livebirth was calculated from the date of entry to the fertility service (for cohort studies) or date of randomisation (for RCTs) to last menstrual period when pregnancy occurred. If last menstrual period was not available, this was estimated with the assumption of term delivery at 40 weeks of gestation. In order to extract the treatment-independent time to natural conception for all cohorts, women were censored at time of treatment, natural conception or end of follow-up, with censoring at whichever of these events occurred first.

Ongoing pregnancy was defined as visualisation of foetal heartbeat by ultrasound after 20 weeks of gestation per woman. In studies defining ongoing pregnancy as a sonographic foetal heartbeat beyond 8 or 12 weeks, we used that definition. Livebirth was defined as delivery of at least one live foetus after 20 weeks of gestation per woman. The occurrence of multiple pregnancies resulting in the birth of more than one baby was considered a single event.

Other secondary outcomes were clinical pregnancy defined as pregnancy diagnosed by ultrasonographic visualisation of one or more gestational sacs or definitive clinical signs of pregnancy, miscarriage defined as the spontaneous loss of an intra-uterine pregnancy prior to 22 completed weeks of gestational age, ectopic pregnancy defined as a pregnancy outside the uterine cavity diagnosed by ultrasound, surgical visualisation or histopathology, and chemical pregnancy defined as pregnancy diagnosed only by the detection of beta hCG in serum or urine (Zegers-Hochschild *et al.*, 2017).

The following other factors known to affect natural fertility were collected: diagnosis, duration of infertility, referral status, BMI, primary versus secondary infertility, semen characteristics (volume, morphology, motility, concentration), cycle length, basal FSH levels, antral follicle count, anti-Müllerian hormone (AMH), tubal status and semen status (Bensdorp *et al.*, 2017).

Data collection and analysis

Search strategy.

The following databases were searched to 1.7.2018: PubMed, MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library, clinicaltrials.gov. Relevant reviews and references lists of included studies were hand searched. The search strategy was documented in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Search terms included 'fertility service', 'waiting list', 'treatment-independent' and 'spontaneous conception'. Language restriction was not applied. Studies prior to the year 2000 were excluded on the basis that the original authors would likely no longer have access to IPD.

Selection of studies.

Two authors (S.J.C. and N.A.D.) independently assessed the included studies, in order to ascertain eligibility for inclusion, extract outcomes of interest and determine the quality of studies. In the event of discrepancies, a third author was introduced (B.W.M.) to form a final decision.

Assessment of risk of bias.

Two authors (S.J.C. and N.A.D.) independently assessed risk of bias of included studies using the following tools:

- The risk of bias assessment tool developed by the Cochrane Collaboration for RCTs (Higgins *et al.*, 2011).
- The Newcastle–Ottawa Scale for cohort studies and case-control studies (Wells *et al.*, 2008).

Disagreements were resolved by discussion and or by input from a third author (B.W.M.).

Data collection.

Corresponding authors of identified studies were contacted and invited to provide IPD. Study protocols were obtained.

Analysis.

All IPD for women aged ≥35 years were combined into a single database, including all available variables corresponding to studied outcomes (as above). We used a Kaplan–Meier curve to show the estimated cumulative natural conception rate per infertility diagnosis group. Cox proportional hazards analysis was conducted to determine which factors were related to time-to-pregnancy for women aged ≥35 years. Scaled Schoenfeld residuals were used to check if the estimated effect of covariates were proportional over time (Grambsch and Therneau, 1994). Restricted cubic spline analysis was used to assess whether there was a linear association between female age as a continuous variable and natural conception leading to ongoing pregnancy or livebirth (Harrell, 2001). The best fit was preferred, judged by a Wald test for non-linear terms and the lowest Akaike Information Criterion (Akaike, 2011). If fits were similar, the simplest model was preferred (i.e. the model with the lowest number of knots or parameters estimated).

In the case where a non-linear association was discovered, the effect of different female ages on livebirth rates, ranging from 35 to 43 years, was visualised in a plot. Using the model with the best fit, absolute chances of natural conception over 6 and 12 months were tabulated for all combinations of patient characteristics.

Sensitivity analyses.

Not all studies had collected data on all covariates, most notably FSH, AMH and semen parameters. Only when data were available from multiple studies, we considered these detailed covariates for analysis or to use in imputation. Otherwise, analysis was restricted to covariates that were available in all studies. To account for the fact that we combined multiple studies using separate study designs, protocols and recruitment in different countries, we used a gamma frailty random effects Cox model. Using this model, we calculated the absolute chances of natural conception over 6 or 12 months and presented these next to the tabulated chances from the Cox model without random effects.

Missing data.

Depending on the extent of missing data on relevant covariates, we used multiple or single imputation.

Software.

Data were prepared in SPSS Statistics (IBM, version 24, Armonk, NY, USA) and Microsoft Excel (Microsoft Office, version 15.41, Redmond, WA, USA), and analysed using R (version 3.3.2, Vienna, Austria) with the *rms*, *survival* and *frailtyEM* packages.

Registration.

The protocol was registered with PROSPERO (CRD42018096552).

Results

Systematic review

The search strategy identified 3191 hits, of which 2224 were left after duplicates were removed (Supplementary Data). After study screening, 130 studies were deemed eligible, of which 28 were excluded as they were published prior to the year 2000. Emails were sent to authors of the remaining studies and authors of 30 studies replied, resulting in 18 unique databases. Upon receipt of the data, nine databases were excluded. Two did not record natural conception outcome as they were from RCTs that only performed an intention-to-treat analysis without recording treatment-independent pregnancies (Steiner *et al.*, 2015), one database was an RCT embedded in a cohort yielding duplicate data (Custers *et al.*, 2012), one database was in a file format that could not be accessed (Mol *et al.*, 2001), and in seven, the treatment-free follow-up time could not be accurately ascertained (Osmanagaoglu *et al.*, 2002; Gnoth *et al.*, 2003; Brandes *et al.*, 2009; Walschaerts *et al.*, 2012; Wynter *et al.*, 2013). This resulted in nine included databases ($n = 4379$ women). The number of women included and excluded based on study selection criteria was presented according to PRISMA guidance (Fig. 1).

Of the included studies, two were RCTs and seven were cohort studies (six prospective, one retrospective). Of the RCTs, two investigated different contrast methods for hysterosalpingography (Lindborg *et al.*, 2009; Dreyer *et al.*, 2017). We included all arms, regardless of contrast used, in the meta-analysis as this was considered part of the diagnostic work-up. Of the cohort studies, one included women who discontinued ART (Cahill *et al.*, 2005), one included women on the waiting list for ART (Eijkemans *et al.*, 2008), and five included all women presenting for fertility services capturing all treatment-related and treatment-independent fertility outcomes during a fixed follow-up interval (van der Steeg *et al.*, 2007; Pinborg *et al.*, 2009; Pearce *et al.*, 2017; Righarts *et al.*, 2017; Rantsi *et al.*, 2018).

Three studies were subgroup analyses from larger cohort studies or RCTs, where for the purposes of the meta-analysis the data from the original study was requested and the related publications were searched for (van der Steeg *et al.*, 2007; Pinborg *et al.*, 2009; Rantsi *et al.*, 2018). Of note, based on local guidelines, some women with intermediate to good prognosis for natural fertility were preferentially counselled for initial expectant management (van der Steeg *et al.*, 2007; Eijkemans *et al.*, 2008; Righarts *et al.*, 2017). Local guidelines and prognostic models used to calculate natural fertility were described, including the Hunault model (Hunault *et al.*, 2004). Women of age $\geq$35 years were smaller subsets of the original studies, ranging from 29 to 1445 (original study sizes ranged from 120 to 7860 participants).

Of the included studies, half were multicentre (four from the Netherlands, one from Denmark) (van der Steeg *et al.*, 2007; Eijkemans *et al.*, 2008; Pinborg *et al.*, 2009; Dreyer *et al.*, 2017), while the others were single-centre studies. All studies originated from high-resourced countries. Six studies reported on livebirth while three reported on pregnancy as the sole primary outcome (van der Steeg *et al.*, 2007; Eijkemans *et al.*, 2008; Pearce *et al.*, 2017). Data from these nine studies were used in the composite primary outcome of livebirth and ongoing pregnancy. Definition of different subgroups of infertility was heterogeneous, including methods described by Hull, assessment according to the guidelines of the Dutch Society of Obstetrics and Gynaecology, local clinical priority access criteria (Hull *et al.*, 1985; Dutch Society of Obstetrics and Gynaecology, 2004; Gillett *et al.*, 2012) and was not described in two studies (Schmidt, 2006; Lindborg *et al.*, 2009).

Of the prognostic factors of interest, all studies with exception of one (Pearce *et al.*, 2017) reported duration of infertility, types of infertility and whether it was primary or secondary infertility. Secondary outcomes were reported in four studies (Cahill *et al.*, 2005; Lindborg *et al.*, 2009; Pinborg *et al.*, 2009; Dreyer *et al.*, 2017), of which two studies reported on multiple pregnancy (Cahill *et al.*, 2005; Dreyer *et al.*, 2017), four reported on rate of miscarriage (Cahill *et al.*, 2005; Schmidt, 2006; Lindborg *et al.*, 2009; Dreyer *et al.*, 2017) and two reported on the rate of ectopic pregnancy (Cahill *et al.*, 2005; Dreyer *et al.*, 2017). Ongoing pregnancy in these studies was defined as foetal cardiac activity on ultrasound on assessment, either at gestation of at least 8 weeks (Eijkemans *et al.*, 2008) or at least 12 weeks (van der Steeg *et al.*, 2007). Data for ongoing pregnancy as defined by the protocol of at least 20 weeks could not be obtained. One study reported time to delivery, where time to conception was estimated with the assumption of term delivery (Righarts *et al.*, 2017). Methodological characteristics of included studies are presented in table form (Table I).

Studies were generally of moderate to high quality (Tables II and III). Most cohort studies included all women presenting to fertility services with a follow-up of up to 13 years for some cohorts and were graded

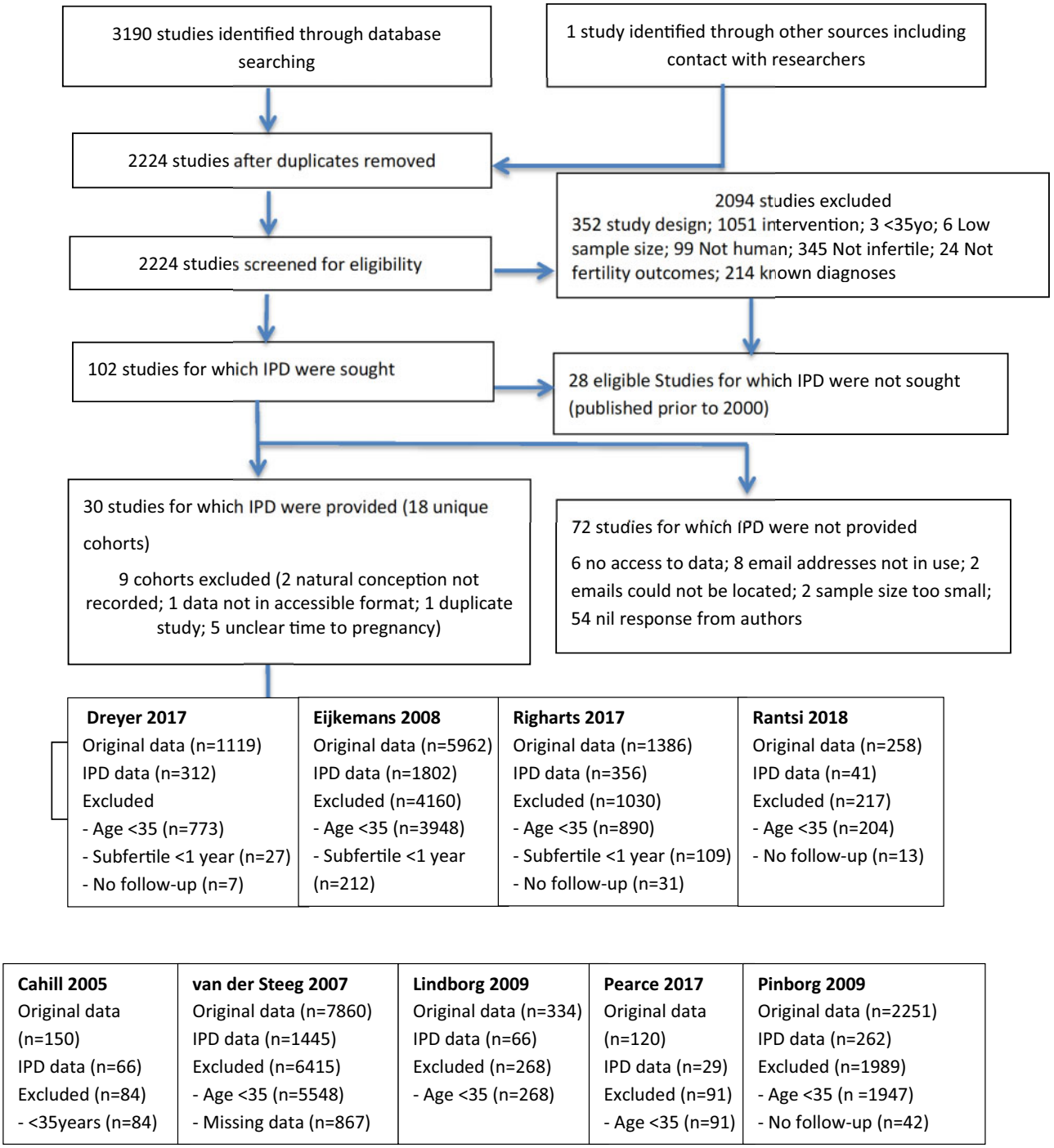


Figure 1 PRISMA individual participant data flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; IPD, individual participant data.

as high quality. This was particularly true for large cohort studies (van der Steeg *et al.*, 2007; Eijkemans *et al.*, 2008; Righarts *et al.*, 2017). RCTs were of high quality with clear method of randomisation and allocation concealment. Given the objective outcomes livebirth or ongoing pregnancy, this was graded as unclear risk of bias despite lack of blinding. A funnel plot could not be used for the detection of publication bias as not all studies were powered to detect natural conception.

Table I Study and methodological characteristics.

	Study design	Setting	Inclusion criteria	Exclusion criteria	Outcomes of interest	Prognostic factors
Cahill *et al.* ($n = 66$)	Prospective cohort	Single centre (UK), 1987–1991	All couples who attended for fertility treatment	Severe male factor Severe tubal factor	Livebirth Multiple pregnancy Ectopic pregnancy Miscarriage	Duration infertile Diagnoses Primary/Secondary
van der Steeg *et al.* ($n = 1445$)	Prospective cohort	Multicentre (Dutch, 38 centres), 2002–2004	All couples who attended for infertility workup	Severe male factor Ovulation disorder	Ongoing pregnancy (USA ≥12 weeks)	Duration infertile Diagnoses Primary/Secondary Sperm, FSH
Dreyer *et al.* ($n = 312$)	RCT	Multicentre (Dutch, 27 centres), 2012–2014	Age 8–39 years, spontaneous menstrual cycles, infertile at least 1 year, indication for hysterosalpingography	Endocrine disorder Severe male factor Severe tubal factor Ovulation disorder	Livebirth Multiple pregnancy Ectopic pregnancy Miscarriage	Duration infertile Diagnoses Primary/Secondary
Eijkemans *et al.* ($n = 1802$)	Prospective cohort	Multicentre (Dutch, nationwide), 2002–2003	All couples who attended for IVF	Non-IVF treatment	Ongoing pregnancy (USA ≥8 weeks)	Duration infertile Diagnoses Primary/Secondary
Righarts *et al.* ($n = 356$)	Prospective cohort	Single centre (New Zealand), 1998–2005	All couples who attended for infertility workup		Livebirth	Duration infertile Diagnoses Primary/Secondary FSH
Lindborg *et al.* ($n = 66$)	RCT	Single centre (Finland), 2001–2006	All couples who attended for infertility workup,including a HyCoSy	Female age >=40 Severe male factor Severe tubal factor Ovulation disorder	Livebirth Miscarriage	Duration infertile Diagnoses Primary/Secondary Sperm
Pearce *et al.* ($n = 29$)	Retrospective cohort	Single centre (Australia), 2013–2016	All couples who attended for infertility workup,including a HyCoSy		Pregnancy	Diagnoses
Rantsi *et al.* ($n = 41$)	Prospective cohort	Single centre (Finland), 2007–2010	All couples who attended for infertility workup		Livebirth	Duration infertile Diagnoses Primary/Secondary
Pinborg *et al.* ($n = 262$)	Prospective cohort	Multicentre (Denmark, 5 centres), 2000-ongoing	All couples who attended for fertility treatment		Livebirth Miscarriage	Duration infertile Diagnoses Primary/Secondary

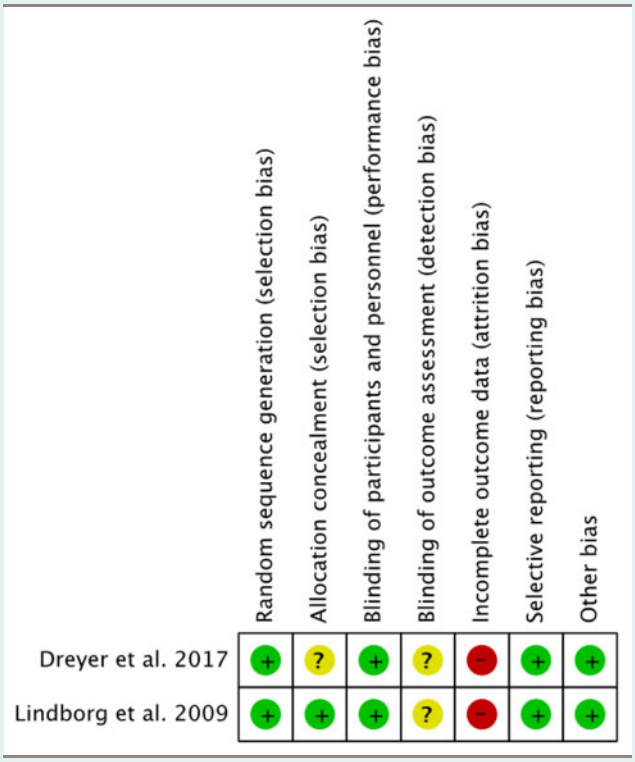
HyCoSy, hysterosalpingography; US, ultrasound; RCT, randomised controlled trial.

Table II Risk of bias grading of cohort studies utilising the Newcastle–Ottawa Scale.

	Selection				Comparability	Outcome		
	1	2	3	4	1	1	2	3
Cahill *et al.*	*	*		*	*		*	
Eijkemans *et al.*	*	*	*	*	*	*	*	*
Righarts *et al.*	*	*	*	*	*	*	*	*
Van der Steeg *et al.*	*	*	*	*	*	*	*	*
Pearce *et al.*		*	*		*		*	*
Pinborg *et al.*	*	*					*	
Rantsi *et al.*	*	*	*	*	*	*	*	*

*The Newcastle Ottawa Scale is graded with a star system, if criteria are fulfilled a star is awarded for each individual question

Table III Risk of bias grading of randomised controlled trials utilising the Cochrane Risk of Bias tool.



IPD meta-analysis

Baseline characteristics of the women are in Table IV. A total of 4379 women from six countries were included of whom median female age was 37.3 years (25th to 75th percentile 36.1–38.9 years). There were little data ($n = 531$) for women over 40 years. Median duration of infertility was 2.4 years (25th to 75th percentile 1.5–4.0 years), of which 2367 (54%) were primary infertility cases. Unexplained infertility accounted for the most infertility at 51.0% ($n = 2233$), followed by

Table IV Characteristics of all included couples by cohort.

	Eijkemans *et al.* *n* = 1802	Van der Steeg *et al.* *n* = 1445	Righarts *et al.* *n* = 356	Dreyer *et al.* *n* = 312	Pinborg *et al.* *n* = 262	Lindborg *et al.* *n* = 66	Cahill *et al.* *n* = 66	Rantsi *et al.* *n* = 41	Pearce *et al.* *n* = 29
Female age, years [median, 25h–75th percentile]	37.4 [36.2, 39.1]	37.4 [36.1, 38.9]	37.8 [36.1, 40.2]	37.1 [36.0, 38.5]	36.0 [35.0, 38.0]	36.3 [35.7–37.2]	38.0 [36.0, 39.0]	36.9 [36.0, 38.1]	38.0 [36.0–39.0]
Duration of infertility, years [median, 25th–75th percentile]	3.2 [2.1, 4.7]	1.6 [1.2, 2.5]	2.9 [1.6, 5.0]	1.8 [1.3, 2.3]	4.0 [3.0, 5.0]	2.0 [1.5–2.5]	5.0 [3.0, 7.0]	1.5 [1.0, 3.0]	8.0 [3.0–11.0]
Primary infertile (%)	944 (52.4)	772 (53.4)	230 (64.6)	182 (58.3)	135 (51.5)	27 (40.9)	43 (65.2)	17 (41.5)	20 (69)
Median follow-up, in months	4.1	5.7	7.6	3.5	7.4	6.0	8.5	9.6	7.0
Types of infertility									
Unexplained infertility (%)	462 (25.6)	1207 (83.5)	86 (24.2)	275 (88.1)	83 (31.7)	66 (100)	9 (14.3)	19 (46.3)	26 (89.7)
Male factor (%)	581 (32.2)	142 (9.8)	114 (32.0)		74 (28.2)		16 (25.4)	3 (7.3)	
Tubal factor (%)	373 (20.7)	96 (6.6)	76 (21.3)	25 (8.0)	64 (24.4)		23 (36.5)	8 (19.5)	2 (6.9)
Endometriosis (%)	106 (5.9)		29 (8.1)				9 (14.3)	6 (14.6)	1 (3.4)
Hormonal/menstrual cycle infertility (%)	109 (6.0)		38 (10.7)		17 (6.5)			4 (9.8)	
Immunological infertility (%)	59 (3.3)								
Uncertain/other (%)	112 (6.2)		13 (3.7)	12 (3.8)	24 (9.2)		6 (9.5)	1 (2.4)	

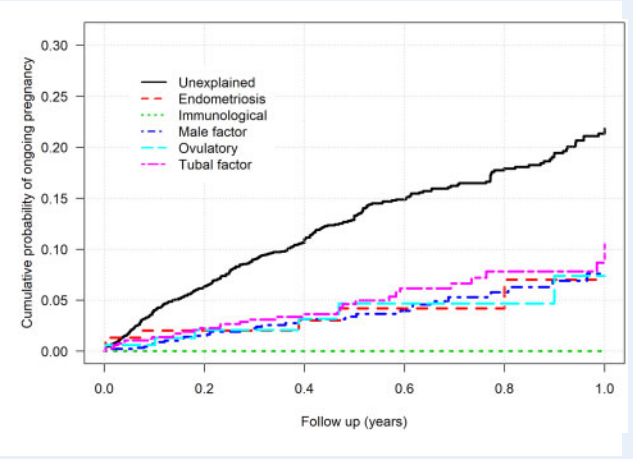


Figure 2 Kaplan–Meier curves depicting the natural rate of conception leading to ongoing pregnancy or livebirth, stratified for the different types of infertility.

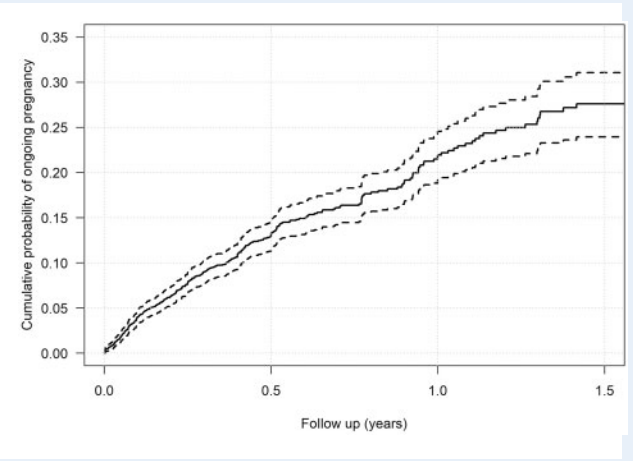


Figure 3 Kaplan–Meier curve depicting the natural rate of conception leading to ongoing pregnancy or livebirth for unexplained infertile couples or unknown diagnoses. Dotted lines are 95% confidence limits.

male factor (21.2%, $n = 930$), tubal factor (15.2%, $n = 667$), ovulatory disorders (3.8%, $n = 168$), endometriosis (3.4%, $n = 151$), immunological causes (1.3%, $n = 59$) and other causes of infertility (3.9%, $n = 171$). Only one study included detailed covariate data, such as AMH and FSH, and therefore, these covariates were not used (van der Steeg *et al.*, 2007). BMI and smoking status were also reported in four studies (van der Steeg *et al.*, 2007; Lindborg *et al.*, 2009; Righarts *et al.*, 2017; Rantsi *et al.*, 2018). Data on the most important factors aside from female age, duration of infertility and primary or secondary infertility, were missing in $n = 32$ (0.7%), which was accounted for using single imputation.

When considering the composite primary outcome of livebirth and ongoing pregnancy, a total of 429 events were noted (9.8%). Any specific diagnosis of infertility was associated with a lower hazard ratio (HR) for natural conception leading to ongoing pregnancy or livebirth compared to unexplained infertility, except for immunological infertility which did not reach statistical significance (HR 0.11; 95% CI 0.01–1.65). HRs for male factor (HR 0.30; 95% CI 0.21–0.43), tubal factor (HR 0.42; 95% CI 0.30–0.60), endometriosis (HR 0.36; 95% CI 0.17–0.76) and ovulation disorders (HR 0.409; 95% CI 0.21–0.76) were significantly lower compared to unexplained infertility. In all infertility subgroups, the probability of natural conception leading to ongoing pregnancy increased over follow-up with the exception of immunological infertility (Fig. 2).

Given the heterogeneity in method of diagnosis and the large availability of robust data for women with unexplained infertility, further analysis of the probability of ongoing pregnancy in these women ($n = 2404$) was performed. For women with unexplained infertility, the Kaplan–Meier estimate of natural conception leading to ongoing pregnancy or livebirth was 13.3% (95% CI 11.7–14.9%) within 6 months and 21.9% (95% CI 19.2–24.5) within 12 months (Fig. 3).

The final Cox model contained female age, duration of infertility and primary or secondary infertility. In the analysis of those with unexplained infertility, the model with non-linear effects for female age and duration of infertility fitted best (using restricted cubic splines with 3 and 4 knots, respectively). The non-linear effect of female age on natural conception leading to ongoing pregnancy is shown (Fig. 4), where the probability of natural conception decreases for women aged 38 years or older. Using this model, a 35-year-old woman with 2 years of primary unexplained infertility had a predicted probability of natural conception of 0.15 (95% CI 0.11–0.19) after 6 months and 0.24 (95% CI 0.17–0.30) after 12 months (Table V). For a woman of age 42 years, this decreased to 0.08 (95% CI 0.04–0.11) after 6 months and 0.13 (95% CI 0.07–0.18) after 12 months. For women with primary unexplained infertility who have been trying to conceive naturally for 5 years, there was very low (<5%) probability of natural conception leading to ongoing pregnancy over 12 months when the woman is 41 years old or above (Table V). The results with the random effects Cox model were more optimistic, estimating higher probabilities of ongoing pregnancy than the Cox model without random effects, and never reaching below 5% over 12 months.

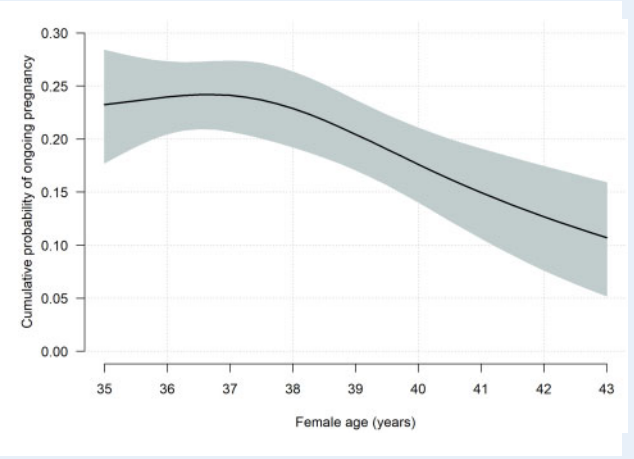


Figure 4 Effect of female age on the probability of natural conception leading to ongoing pregnancy or livebirth within 12 months. Grey areas indicate 95% confidence limits.

Table V Predicted probabilities of natural conception over 6 or 12 months for couples with unexplained infertility for various combinations of female age, duration of infertility and primary or secondary infertility.

Female age (years)	Duration of infertility (years)	Primary or secondary infertility	Predicted probability over 6 months (95%CI)	Predicted probability over 12 months (95%CI)	Predicted probability over 6 months (frailty)*	Predicted probability over 12 months (frailty)*
35	1	Primary	0.18 (0.12–.24)	0.29 (0.20–0.37)	0.23	0.37
36	1	Primary	0.19 (0.14–0.23)	0.30 (0.23–0.36)	0.24	0.38
37	1	Primary	0.19 (0.14–0.23)	0.30 (0.23–0.36)	0.24	0.38
38	1	Primary	0.17 (0.13–0.22)	0.28 (0.21–0.34)	0.23	0.36
39	1	Primary	0.15 (0.11–0.19)	0.25 (0.19–0.31)	0.20	0.32
40	1	Primary	0.13 (0.09–0.17)	0.22 (0.16–0.27)	0.17	0.28
41	1	Primary	0.11 (0.07–0.15)	0.18 (0.12–0.24)	0.14	0.23
42	1	Primary	0.09 (0.05–0.13)	0.15 (0.09–0.22)	0.12	0.20
35	2	Primary	0.15 (0.11–0.19)	0.24 (0.17–0.30)	0.18	0.29
36	2	Primary	0.15 (0.12–0.18)	0.25 (0.19–0.29)	0.18	0.30
37	2	Primary	0.15 (0.12–0.18)	0.25 (0.19–0.29)	0.18	0.30
38	2	Primary	0.14 (0.11–0.17)	0.23 (0.18–0.28)	0.17	0.28
39	2	Primary	0.13 (0.10–0.16)	0.21 (0.16–0.25)	0.15	0.25
40	2	Primary	0.11 (0.08–0.14)	0.18 (0.13–0.22)	0.13	0.21
41	2	Primary	0.09 (0.06–0.12)	0.15 (0.10–0.20)	0.11	0.18
42	2	Primary	0.08 (0.04–0.11)	0.13 (0.07–0.18)	0.09	0.15
35	3	Primary	0.08 (0.06–0.11)	0.14 (0.09–0.18)	0.11	0.18
36	3	Primary	0.09 (0.06–0.11)	0.14 (0.11–0.17)	0.11	0.19
37	3	Primary	0.08 (0.06–0.11)	0.14 (0.11–0.17)	0.11	0.19
38	3	Primary	0.08 (0.06–0.10)	0.13 (0.10–0.17)	0.10	0.18
39	3	Primary	0.07 (0.05–0.09)	0.12 (0.09–0.15)	0.09	0.16
40	3	Primary	0.06 (0.04–0.08)	0.10 (0.07–0.13)	0.08	0.13
41	3	Primary	0.05 (0.03–0.07)	0.08 (0.05–0.11)	0.06	0.11
42	3	Primary	0.04 (0.02–0.06)	0.07 (0.04–0.10)	0.05	0.09
35	4	Primary	0.06 (0.03–0.08)	0.09 (0.06–0.13)	0.08	0.13
36	4	Primary	0.06 (0.04–0.08)	0.10 (0.06–0.13)	0.08	0.14
37	4	Primary	0.06 (0.04–0.08)	0.10 (0.06–0.13)	0.08	0.14
38	4	Primary	0.05 (0.04–0.07)	0.09 (0.06–0.12)	0.07	0.13
39	4	Primary	0.05 (0.03–0.06)	0.08 (0.05–0.11)	0.06	0.11
40	4	Primary	0.04 (0.02–0.05)	0.07 (0.04–0.09)	0.05	0.09
41	4	Primary	0.03 (0.02–0.05)	0.06 (0.03–0.08)	0.04	0.08
42	4	Primary	0.03 (0.01–0.04)	0.05 (0.02–0.07)	0.04	0.06
35	5	Primary	0.05 (0.03–0.07)	0.08 (0.05–0.11)	0.07	0.11
36	5	Primary	0.05 (0.03–0.07)	0.08 (0.05–0.11)	0.07	0.12
37	5	Primary	0.05 (0.03–0.07)	0.08 (0.05–0.11)	0.07	0.12
38	5	Primary	0.05 (0.03–0.06)	0.08 (0.05–0.10)	0.06	0.11
39	5	Primary	0.04 (0.02–0.05)	0.07 (0.04–0.09)	0.06	0.09
40	5	Primary	0.03 (0.02–0.05)	0.06 (0.03–0.08)	0.05	0.08
41	5	Primary	0.03 (0.02–0.04)	0.05 (0.03–0.07)	0.04	0.07
42	5	Primary	0.02 (0.01–0.04)	0.04 (0.02–0.06)	0.03	0.05
35	6	Primary	0.05 (0.03–0.07)	0.08 (0.04–0.11)	0.06	0.11
36	6	Primary	0.05 (0.03–0.07)	0.08 (0.05–0.11)	0.06	0.11
37	6	Primary	0.05 (0.03–0.07)	0.08 (0.05–0.11)	0.06	0.11
38	6	Primary	0.04 (0.03–0.06)	0.07 (0.05–0.10)	0.06	0.10
39	6	Primary	0.04 (0.02–0.05)	0.07 (0.04–0.09)	0.05	0.09
40	6	Primary	0.03 (0.02–0.05)	0.06 (0.03–0.08)	0.04	0.08

(continued)

Table V Continued

Female age (years)	Duration of infertility (years)	Primary or secondary infertility	Predicted probability over 6 months (95%CI)	Predicted probability over 12 months (95%CI)	Predicted probability over 6 months (frailty)*	Predicted probability over 12 months (frailty)*
41	6	Primary	0.03 (0.01–0.04)	0.05 (0.02–0.07)	0.04	0.06
42	6	Primary	0.02 (0.01–0.03)	0.04 (0.02–0.06)	0.03	0.05
35	1	Secondary	0.22 (0.15–0.29)	0.35 (0.25–0.44)	0.28	0.44
36	1	Secondary	0.23 (0.17–0.28)	0.36 (0.28–0.43)	0.29	0.45
37	1	Secondary	0.23 (0.18–0.28)	0.36 (0.28–0.43)	0.29	0.45
38	1	Secondary	0.22 (0.16–0.26)	0.34 (0.26–0.41)	0.28	0.43
39	1	Secondary	0.19 (0.15–0.23)	0.30 (0.24–0.37)	0.24	0.38
40	1	Secondary	0.16 (0.12–0.20)	0.26 (0.20–0.32)	0.21	0.33
41	1	Secondary	0.14 (0.09–0.18)	0.22 (0.15–0.29)	0.17	0.28
42	1	Secondary	0.12 (0.07–0.16)	0.19 (0.11–0.26)	0.14	0.24
35	2	Secondary	0.18 (0.13–0.23)	0.29 (0.21–0.37)	0.22	0.35
36	2	Secondary	0.19 (0.15–0.23)	0.30 (0.24–0.36)	0.23	0.36
37	2	Secondary	0.19 (0.15–0.23)	0.30 (0.24–0.36)	0.23	0.36
38	2	Secondary	0.18 (0.14–0.21)	0.28 (0.22–0.34)	0.21	0.34
39	2	Secondary	0.16 (0.12–0.19)	0.25 (0.19–0.31)	0.19	0.30
40	2	Secondary	0.13 (0.10–0.17)	0.22 (0.16–0.27)	0.16	0.26
41	2	Secondary	0.11 (0.07–0.15)	0.18 (0.12–0.24)	0.13	0.22
42	2	Secondary	0.09 (0.05–0.13)	0.15 (0.09–0.22)	0.11	0.18
35	3	Secondary	0.10 (0.07–0.13)	0.17 (0.12–0.22)	0.14	0.23
36	3	Secondary	0.11 (0.08–0.13)	0.17 (0.13–0.21)	0.14	0.23
37	3	Secondary	0.11 (0.08–0.13)	0.17 (0.13–0.21)	0.14	0.23
38	3	Secondary	0.10 (0.07–0.12)	0.16 (0.12–0.20)	0.13	0.22
39	3	Secondary	0.09 (0.06–0.11)	0.15 (0.11–0.18)	0.11	0.19
40	3	Secondary	0.07 (0.05–0.09)	0.12 (0.09–0.16)	0.10	0.16
41	3	Secondary	0.06 (0.04–0.08)	0.10 (0.07–0.14)	0.08	0.14
42	3	Secondary	0.05 (0.03–0.07)	0.09 (0.05–0.12)	0.07	0.11
35	4	Secondary	0.07 (0.04–0.10)	0.12 (0.07–0.16)	0.10	0.16
36	4	Secondary	0.07 (0.05–0.10)	0.12 (0.08–0.16)	0.10	0.17
37	4	Secondary	0.07 (0.05–0.10)	0.12 (0.08–0.16)	0.10	0.17
38	4	Secondary	0.07 (0.04–0.09)	0.11 (0.07–0.15)	0.09	0.16
39	4	Secondary	0.06 (0.04–0.08)	0.10 (0.07–0.13)	0.08	0.14
40	4	Secondary	0.05 (0.03–0.07)	0.08 (0.05–0.11)	0.07	0.12
41	4	Secondary	0.04 (0.02–0.06)	0.07 (0.04–0.10)	0.06	0.10
42	4	Secondary	0.03 (0.02–0.05)	0.06 (0.03–0.09)	0.05	0.08
35	5	Secondary	0.06 (0.03–0.08)	0.10 (0.06–0.14)	0.08	0.14
36	5	Secondary	0.06 (0.04–0.08)	0.10 (0.06–0.14)	0.08	0.14
37	5	Secondary	0.06 (0.04–0.08)	0.10 (0.06–0.14)	0.08	0.14
38	5	Secondary	0.06 (0.04–0.08)	0.10 (0.06–0.13)	0.08	0.14
39	5	Secondary	0.05 (0.03–0.07)	0.08 (0.05–0.11)	0.07	0.12
40	5	Secondary	0.04 (0.03–0.06)	0.07 (0.04–0.10)	0.06	0.10
41	5	Secondary	0.04 (0.02–0.05)	0.06 (0.03–0.09)	0.05	0.08
42	5	Secondary	0.03 (0.01–0.04)	0.05 (0.02–0.08)	0.04	0.07
35	6	Secondary	0.06 (0.03–0.08)	0.10 (0.05–0.14)	0.08	0.14
36	6	Secondary	0.06 (0.04–0.08)	0.10 (0.06–0.14)	0.08	0.14
37	6	Secondary	0.06 (0.04–0.08)	0.10 (0.06–0.14)	0.08	0.14
38	6	Secondary	0.06 (0.03–0.08)	0.09 (0.06–0.13)	0.08	0.13
39	6	Secondary	0.05 (0.03–0.07)	0.08 (0.05–0.11)	0.07	0.11

(continued)

Table V Continued

Female age (years)	Duration of infertility (years)	Primary or secondary infertility	Predicted probability over 6 months (95%CI)	Predicted probability over 12 months (95%CI)	Predicted probability over 6 months (frailty)*	Predicted probability over 12 months (frailty)*
40	6	Secondary	0.04 (0.02–0.06)	0.07 (0.04–0.10)	0.06	0.09
41	6	Secondary	0.03 (0.02–0.05)	0.06 (0.03–0.08)	0.04	0.08
42	6	Secondary	0.03 (0.01–0.04)	0.05 (0.02–0.07)	0.04	0.06

*The final two columns are average predictions from the Cox model including a random effect (frailty) for cohort. Note that the confidence limits of the latter are undefined.

Three studies recorded time to treatment and treatment-related outcomes (Schmidt, 2006; Righarts *et al.*, 2017; Rantsi *et al.*, 2018). Given the heterogeneity in types of treatment the women received, the different starting times of treatment after recruitment that does not allow a direct comparison and the relatively small numbers involved, the effect of treatment was not estimated, in keeping with the original protocol.

Discussion

Summary of findings

This study was designed to guide treatment strategies for women of age ≥35 years presenting to a fertility service. As expected, natural fertility declined with female age. This association between female age and time to natural conception leading to ongoing pregnancy or livebirth was non-linear. Studies were of moderate to high quality and mainly derived from high resource settings. Of note, any diagnosis of infertility conferred a poorer prognosis compared with unexplained infertility.

Strengths and limitations

The IPD meta-analysis method was used to incorporate all available data on women aged 35 years or above to estimate more accurately their probability of a natural conception leading to ongoing pregnancy or livebirth. The most important limitation in our study is the aggregation of studies that used different study design, recruitment strategies in different centres, protocols and countries. In addition, as this was an undifferentiated population of women, with heterogeneous methods used in defining tubal status, male infertility and ovulatory status, the most robust conclusions could only be made for those with unexplained infertility. Additionally, only one study reported on outcomes from immunological infertility (Eijkemans *et al.*, 2008). The frailty model was utilised in order to account for these differences. This resulted in higher point estimates and undefined CIs, however, did not change the relationship between age and time to natural conception.

Limited confounding variables (diagnoses, duration of infertility and whether infertility was primary or secondary) were included in the analysis, however, other known variables that could potentially impact on fertility (e.g. AMH, BMI) were insufficient. Additionally, data on secondary outcomes, such as multiple pregnancy and ectopic pregnancy, were negligible.

The effect of treatment was not an area of interest that was explored in this study. In order to provide the best model for clinical decision-making, we have elected to study only natural conception in the absence of treatment. This is because the effect of treatment would likely act as a competing risk, resulting in a reduction in detected rates of natural conception. This was addressed by censoring women at the time when treatment occurred. However, due to this censorship, follow-up time was significantly truncated for many women included in this IPD analysis, as some would have commenced treatment at an earlier date before natural conception occurred.

The major contributors to our study came from Dutch data, in which some patients with intermediate to good prognosis for natural conception were preferentially counselled for expectant management, although this did not seem to introduce a strong confounding effect (van Geloven *et al.*, 2014). Also, addition of the RCTs introduced strict inclusion and exclusion criteria, where severe male infertility and tubal pathology were excluded (Lindborg *et al.*, 2009; Dreyer *et al.*, 2017). Unfortunately, there were little data for women above the age of 40 years.

Clinical implications

Female age is a strong predictor of infertility, which also is reflected in the fact that increasing age predicts poorer outcomes for ART (Malchau *et al.*, 2017; Centers for Disease Control and Prevention ASfRM and Society for Assisted Reproductive Technology, 2018; Fitzgerald *et al.*, 2019). In addition, it is unclear whether ART adds any meaningful increase in livebirth rate on top of natural fertility for certain diagnoses (McLernon *et al.*, 2016; van Eekelen *et al.*, 2019). Moreover, the costs and adverse effects, such as multiple livebirth rate, warrant objective evaluation of ART use/recommendations.

On a global scale, older women account for a significant proportion of ART usage. In 2011, a study incorporating 2560 centres from 65 countries discovered that women who were at least 35 years old accounted for 60% of ART usage (Adamson *et al.*, 2018). In 2016, this percentage remained stable at 61–62% in women from high resource settings (Centers for Disease Control and Prevention ASfRM and Society for Assisted Reproductive Technology, 2018; Fitzgerald *et al.*, 2019). Treatment decisions are also influenced by reimbursement policies, which may impose age restrictions. In addition, there have been no RCTs investigating treatment versus no treatment in a cohort of this age. Existing data tend to report per cycle outcomes and do not take into account the dropout rate of women attending fertility services, which may skew fertility outcomes.

Women attending fertility services should be encouraged to pursue natural conception while waiting for treatment commencement, as well as during treatment, and not give up on their fertility even after treatment fails (Walschaerts *et al.*, 2012; Wynter *et al.*, 2013). Women of advanced maternal age with low natural fertility chances as well as low chances from treatment could potentially be counselled for donor oocyte treatment (Hogan *et al.*, 2019). Clearly, natural fertility remains an important source of livebirth and ongoing pregnancy, and should not be neglected in the context of clinical counselling and research, especially for women with unexplained infertility.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Authors' roles

S.J.V., R.V.E., M.V.W., D.J.M. and B.W.J.M. were involved in the drafting of the protocol. S.J.C. and N.A.D. were involved in study selection and risk of bias assessment. S.J.C., R.V.E., M.H.M., D.J.M., I.C., E.L., K.D., D.J.C., W.R.G., A.R., A.S., T.R., L.S. and R.M.J.C.E. were involved in data analysis. S.J.C. and R.V.E. were responsible for the final draft of the manuscript. All authors critically revised the manuscript and approved the final manuscript.

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Conflict of interest

B.W.M. reports consultancy for ObsEva, Merck, Merck KGaA, iGenomix and Guerbet. B.W.M. reports research support by Merck and Guerbet. The remaining authors do not declare any conflicts on interest.

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