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Meta-Analysis

Reproductive epidemiology

How common is natural conception in women who have had a livebirth via assisted reproductive technology? Systematic review and meta-analysis

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ABSTRACT

STUDY QUESTION: What is the proportion of women who experience natural conception after a livebirth via assisted reproductive technology (ART)?

SUMMARY ANSWER: Current evidence suggests that natural conception pregnancy may occur in at least one in five women after having a baby via IVF or ICSI.

WHAT IS KNOWN ALREADY: It is widely known that some women having babies via ART go on to conceive naturally. This reproductive history is of media interest and often described as 'miracle' pregnancies.

STUDY DESIGN, SIZE, DURATION: A systematic review with meta-analysis was carried out. Ovid Medline, Embase, and PsycINFO were searched until 24 September 2021 for English language, human studies from 1980. Search terms were used for the concepts of natural conception pregnancy, assisted reproduction, and livebirth.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The inclusion criterion was studies with an outcome measure of the proportion of women experiencing natural conception pregnancy after an ART livebirth. Quality of studies was assessed using the Critical Appraisal Skills Programme cohort study checklist or AXIS Appraisal tool for cross-sectional studies, and a risk of bias assessment was carried out. No studies were excluded based on quality. Random-effects meta-analyses were adopted to produce a pooled effect estimate of the proportion of natural conception pregnancy after ART livebirth.

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 1108 distinct studies were identified, resulting in 54 studies after screening by title and abstract. Eleven studies including 5180 women were selected for this review. The included studies were mostly of moderate quality with a maximum follow-up period ranging from 2 to 15 years. Four studies reported natural conception livebirths which were used as known underestimates of natural conception pregnancies. The pooled estimate for the proportion of women having natural conception pregnancies after ART livebirth was 0.20 (95% CI, 0.17–0.22).

LIMITATIONS, REASONS FOR CAUTION: The studies varied widely according to methodology, population, cause of subfertility, type and outcome of fertility treatment, and length of follow-up, leading to potential bias relating to confounding, selection bias, and missing data.

WIDER IMPLICATIONS OF THE FINDINGS: Current evidence suggests that contrary to widely held views, natural conception pregnancy after ART livebirth is far from rare. National, data-linked studies are needed to provide more accurate estimates of this incidence and analysis of associated factors and trends over time to facilitate tailored counselling of couples considering further ART.

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Introduction

The use of assisted reproductive technology (ART) has increased dramatically in high-income countries since the inception of IVF in 1978 (Human Fertilisation and Embryology Authority (HFEA), 2021), mirroring the trend in increasing age at conception (Office for National Statistics (ONS), 2020) and availability of ART (Lazzari, 2021). More than 10 million babies worldwide have been born to date using IVF (ESHRE, 2022) with 1–6% of babies born per year in the developed world by 2020 (Pinborg, 2019; Richardson, 2020). Infertility is defined by the failure to achieve a pregnancy

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after 12 months or more of regular unprotected sexual intercourse (ICD-11, 2018) and is estimated to affect 1 in 7 heterosexual couples (National Institute for Health and Care Excellence (NICE), 2018). Although the terms 'subfertility' and 'infertility' are often used interchangeably and synonymously with sterility (Gnoth, 2005), it is important to recognize that women seeking and undergoing fertility treatment are not absolutely nor permanently infertile. Over 80% of couples in the general population will conceive naturally within one year; of those who do not conceive in the first year, about half will go on to do so in the second year (NICE, 2013 (last updated 2017)).

IVF was initially developed as a treatment for bilateral tubal occlusion (Steptoe and Edwards, 1978) but is now used for a wide range of causes, including ovulatory disorders, tubal factors, uterine factors, male factors, joint subfertility, and unexplained subfertility. In the UK, current guidance by the National Institute for Health and Care Excellence (NICE) recommends IVF as treatment for prolonged unresolved infertility (National Institute for Health and Care Excellence (NICE), 2013 (last updated 2017)) and IVF is now used for most causes of subfertility including those of potentially lesser severity and duration (Eijkemans *et al.*, 2008). Similarly, the assisted reproductive technique of intracytoplasmic sperm injection (ICSI) was initially used to treat severe forms of male-factor subfertility only, but now it is also used to treat mild male factor, mixed male/female, and unexplained subfertility (Geng *et al.*, 2020). Unexplained subfertility accounted for 32% of all recorded reasons for IVF treatment cycles being carried out in the UK in 2014–2016 (Human Fertilisation and Embryology Authority (HFEA), 2018). Couples with unexplained subfertility have chances of natural conception of up to 63% over the following year according to a 2017 prospective cohort study conducted in the Netherlands (van Eekelen, 2017).

Wider social and legal changes have also led to increasingly diverse reasons for the use of IVF including those by women who may not have experienced fertility problems. In 2018, of all IVF treatment cycles in the UK, 3.1% were undertaken by women in same-sex relationships, 2% were for single women using donor sperm, and 0.5% were for surrogate (Human Fertilisation and Embryology Authority (HFEA), 2020). While heterosexual partnerships are still the majority group, it is the group that is growing most slowly. In addition, 1% of IVF treatment cycles are now for couples seeking to screen for serious genetic conditions that exist in their families using preimplantation genetic diagnosis (PGD) and the number of conditions that can be detected by these methods is steadily increasing.

It is widely known that some women having ART go on to conceive naturally in time (Canning, 2017) and this reproductive history is of media interest. Frequent press articles profile women and celebrities with this experience (Parents, 2023; Anonymous, 2020; Buzzfeed, 2020; Horsager-Boehrer, 2020; Maykin, 2020; Moss, 2020; Gurevich, 2021; Hello!, 2021) often describing their subsequent natural conception pregnancies as 'amazing' or 'miracle' pregnancies, assumed by some to be a universal 'blessing'. Women conceiving spontaneously after ART livebirth also identify themselves as a rarity and their subsequent pregnancies have been seen to include rapid-repeat, unplanned, and unwelcomed pregnancies (Anonymous, 2020; Thwaites, 2022). This systematic review and meta-analysis aim to identify, appraise, and synthesize the current evidence on the incidence of natural conception pregnancy after ART livebirth.

Materials and methods

Ovid Medline, Embase, and PsycINFO were searched on 24 September 2021 for studies with an outcome measure of the proportion of women experiencing natural conception pregnancy after ART livebirth. A search strategy containing thesaurus and free text terms was used for the concepts of (i) natural conception pregnancy, (ii) livebirth, and (iii) assisted conception (IVF and ICSI). The reproducible searches are included in Supplementary Data File S1. The search was limited to the English language, human studies, and publications dating from 1 January 1980. In addition, the Cochrane library was searched for reviews or trials currently in progress and citation searches were undertaken manually of key references to identify additional studies. The websites for the Human Fertilisation and Embryology Authority (HFEA) and European Society of Human Reproduction and Embryology (ESHRE) were also searched for relevant literature.

The results were de-duplicated and managed in EndNote X9. Duplicates were removed using EndNote's duplicate identification strategy and then using the 13-step process outlined in the London School of Hygiene and Tropical Medicine library services blog (London School of Hygiene and Tropical Medicine Library & Archives Service, 2018). These were then screened by title and abstract and subsequently by full text by A.T. and J.H. for studies with an outcome measure of the proportion of women having natural conception pregnancy after ART Livebirth.

Data on study characteristics, design, and results were extracted into Microsoft Excel by A.T. and cross-checked by J.H. using a template designed for this review. These were assessed using the Critical Appraisal Skills Programme cohort study checklist (Critical Appraisal Skills Programme, 2019) and AXIS Appraisal tool for cross-sectional studies (Downes, 2016), exploring the representativeness of the sample, validity of data collection, and the significance, generalizability, and applicability of findings. A risk of bias assessment was also carried out (ROBINS-E Development Group, 2022). No studies were excluded based on quality. Data were imported to Stata 15 software for meta-analyses. The numbers of women having ART livebirths in each sample and the subset of those women having subsequent natural conception pregnancies were used to calculate the proportion of natural conception pregnancy after ART livebirth. Where the number of subsequent natural conception pregnancies was not available, the number of subsequent natural conception livebirths was used. Due to the heterogeneity of studies, random-effects proportional meta-analyses were adopted to produce a pooled effect estimate of the incidence of natural conception pregnancy after ART livebirth. Subgroup analyses based on outcome measure (subsequent spontaneous livebirth or spontaneous pregnancy), type of ART (IVF only, ICSI only, or mixed), length of follow-up (<5 years, 5–10, or over 10 years), and sensitivity analyses (extracting where possible data across the studies at set time points of 2- and 3-year follow-up and excluding the studies with very high risk of bias) were conducted.

Results

There were 11 studies including 5180 women selected for this review. The identification and screening process is summarized in Fig. 1, a PRISMA 2020 flowchart (Page, 2021). The studies varied widely according to methodology, outcome measure (pregnancy or live birth), population (e.g. location, reasons for ART), type and date of fertility treatment, and length of follow-up (Tables 1 and 2) making direct comparisons difficult. Seven included studies were retrospective, longitudinal studies using postal or telephone questionnaires, three were prospective studies (from which we selected relevant subgroups and analysed as nested retrospective cohorts), and there was a single, cross-sectional online survey.

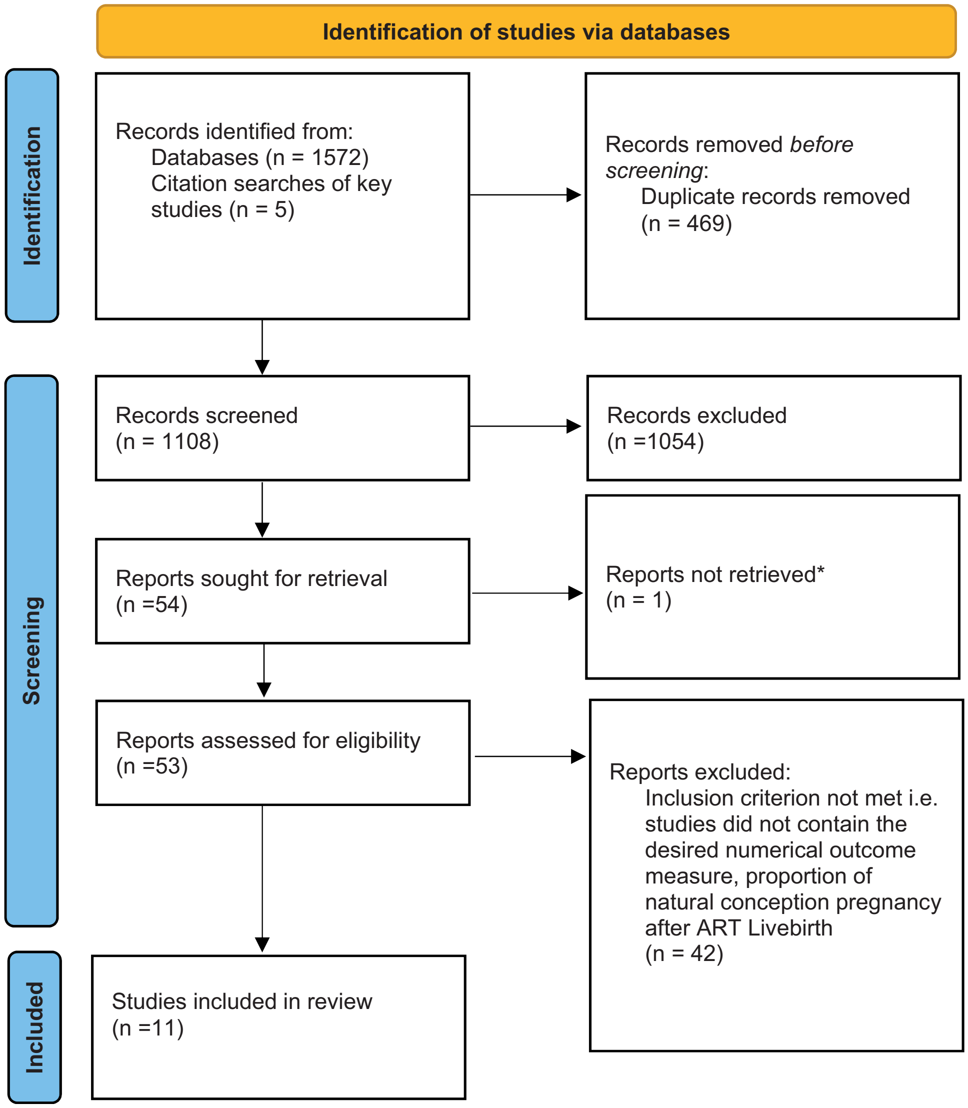

Figure 1. PRISMA flowchart of a systematic review. *Full text unavailable despite interlibrary loan request made to The British Library. The abstract described a review study with no report of the outcome of interest.

Estimating the proportion of women having a natural conception pregnancy after ART was not always a primary objective of the included studies and the women having ART livebirths were often subgroups of larger cohorts set up for other studies (Olivennes, 1997; Ludwig, 2008). Four studies reported natural conception livebirths rather than natural conception pregnancies.

A couple of the earliest studies (Olivennes, 1997; Shimizu, 1999) predate the advent of ICSI and therefore the women in these studies had IVF only, while eight studies consider a mixed sample of women having IVF or ICSI but contain variable proportions of women having births via ICSI, and in some cases, the proportion of IVF and ICSI is not given (Wynter, 2013; Volgsten and Schmidt, 2017). A single study included in this review considered ICSI only, mostly for cases of severe oligoasthenoteratozoospermia (Ludwig, 2008). The largest study (Troude *et al.*, 2012) had a population in which 97% had successful IVF and 3% had births following other fertility treatments, mainly artificial Intrauterine Insemination (IUI) with partner or donor sperm.

The proportions of women having a natural conception pregnancy or livebirth after an ART livebirth ranged from 12% to 33% with an apparent trend towards higher values in more recent studies (Table 1). Seven studies found the majority of the natural conception pregnancies occurred within the first 2–3 years after IVF/ICSI livebirth (Shimizu, 1999; Hennelly, 2000; Ludwig, 2008; Lande, 2012; Wynter, 2013; Marcus *et al.*, 2016; ElMokhallalati, 2019). The study reporting the highest proportion of spontaneous conceptions (Wynter, 2013) found no significant difference between a comparator group of women who had conceived their first child spontaneously.

The included studies were mostly of moderate quality as assessed using the Critical Appraisal Skills Programme (CASP) cohort study checklist (Critical Appraisal Skills Programme, 2019) or AXIS Appraisal tool for cross-sectional studies (Downes, 2016) in Supplementary Tables S1 and S2 respectively. The risk of bias was specifically assessed and a 'traffic light' plot of the domain-level judgements for each individual study is shown in Fig. 2 (McGuinness and Higgins, 2021). The majority of potential bias across the studies related to the domains of confounding, selection bias, and missing data. The salient outcome measures of pregnancy and birth were less susceptible to the inherent risk of recall bias of retrospective, longitudinal studies and so the domain of measurement of the outcome was globally low. The risk of bias associated with the

Table 1. Characteristics of included studies.

First author and year	Date of ART resulting in livebirth (unless other recruitment date specified)	Study location	Study design	Follow-up period (max), years	Data collection	Response rate (%)	Relevant outcome measure	ART	No. of women in sample having IVF/ICSI livebirth (X)	No. of women having subsequent spontaneous pregnancy/livebirth (Y)	Proportion of women having spontaneous pregnancy/livebirth after IVF/ICSI livebirth (X/Y)	Distribution of spontaneous pregnancies over time since IVF/ICSI livebirth
Olivennes, 1997	June 1981–December 1988	Antoine Beclere Hospital Clamart, France	Retrospective cohort	13	Questionnaire completed by post or telephone	87	Spontaneous pregnancy	IVF only	280	33	0.12	No information
Shimizu, 1999	October 1988–November 1994[1]	Akita university hospital, Japan	Retrospective cohort	5	Hospital records and telephone interview	Not quoted	Spontaneous pregnancy	IVF only	142	25	0.18	'Most occurred within 24 months' (~85% cumulative conception rate curve included)
Hennelly, 2000	July 1990–March 1998	Rotunda Hospital, Dublin Ireland	Retrospective cohort	8	Questionnaire completed by post or telephone	97	Spontaneous pregnancy	IVF/ICSI	513	106	0.21	All within 2 years of successful IVF/ICSI
Ludwig, 2008	August 1998–August 2000[2]	59 IVF centres, Germany	Retrospective cohort	6	Questionnaire completed by post or telephone	56	Spontaneous pregnancy	ICSI only	695	139	0.20	74.5% within 2 years of delivery of ICSI conceived infant. Approximately 90% by 3 years (cumulative plot included)
Pinborg, 2009	January 2000–August 2001[3]	4 hospital-based tertiary care reproductive centres, Denmark	Prospective longitudinal record linkage study	5	Postal questionnaire and data linkage to the national medical birth register	75	Spontaneous pregnancy	IVF/ICSI	475	94	0.20	No information
Lande, 2012	January 2001–December 2002	Sheba medical centre, Israel	Retrospective cohort	7	Medical records and telephone interview	78	Spontaneous livebirth	IVF/ICSI	102	22	0.22	63.6% within 18 months of first IVF/ICSI birth; 91% within 3 years
Troude *et al.*, 2012	2000–2002	8 IVF Centres, France	Retrospective cohort	9	Postal questionnaire	57	Spontaneous livebirth	IVF/ICSI/IUI	1320	218	0.17	14% by 2 years 44% by 3 years 87% by 5 years (distribution of births over time histogram included).
Wynter, 2013	2007–2010[4]	ART clinics and maternity units in Melbourne and Sydney, Australia	Prospective cohort study	2	Telephone interview and self-report questionnaires	55 response rate. (21% loss to follow-up)	Spontaneous pregnancy	IVF/ICSI	141	46	0.33	all within 2 years (study follow-up period)
Marcus *et al.*, 2016	June–July 2013[4]	Worldwide (39% participants UK)	Cross-sectional study	6	Internet-based survey	–	Spontaneous pregnancy	IVF/ICSI	253	63	0.25	87% within 2 years (82% within 2 years quoted in abstract).
Volgsten and Schmidt, 2017	2005–2007	Uppsala University Hospital, Sweden	Prospective cohort study	5	Postal questionnaire	63	Spontaneous livebirth	IVF/ICSI	199	52	0.26	No information
ElMokhallalati, 2019	January 1998–December 2011	Aberdeen Fertility clinic, UK	Retrospective cohort	15	Data linkage of electronic records from a fertility centre and national assisted reproduction and maternity databases	–	Spontaneous livebirth	IVF/ICSI	1060	151	0.14	Approximately 70% of births in first 2 years using cumulative treatment-independent livebirth rate curve

[1] Date of IVF livebirth.
[2] Date when pregnant via ICSI.
[3] Date when referred for fertility treatment.
[4] Date of recruitment to study/cross-sectional survey.

Table 2. Characteristics of participants.

First author and year	Age (years)	Indication for ART	Duration of infertility	Type of infertility	Type of ART	No. embryo transfer episodes
Olivennes, 1997	No information given	No information given	No information given	No information given	IVF	No information given
Shimizu, 1999	Mean 32.3, s.d. 3.2, range 24–40	Endometriosis, mild male factor, or unexplained	Mean 5.2 years, s.d. 2.6 years, range 1–14 years	No information given	IVF	No. of IVF treatments: mean 2.2, s.d. 1.4, range 1–8
Hennelly, 2000	Median 34, range unrestricted	Unexplained, tubal factor, male factor, endometriosis, anovulatory, cervical factor	Mean 4, max >15	407 (79%) primary infertility	469 91%, IVF/44, 9% ICSI	No information given
Ludwig, 2008[1]	No information given	Severe oligoasthenotheratozoospermia (80%), obstructive azoospermia (2%), non-obstructive azoospermia (3%), failed fertilization in IVF (8%), others (6%)	No information given	Primary/secondary (split not given)	ICSI	No information given
Pinborg, 2009[2]	Mean 31.8, s.d. 3.5	Unexplained (31%), male factor (30%), tubal pathology (18%), male and female (9%), ovulatory (6%), female (2%), missing (4%)	Mean 4.1 years, s.d. 2.3 years	556 (68%) primary infertility	IVF (45.5%), ICSI (22.2%), IUI (20%), frozen embryo replacement (9.6), others (1%), missing (1%)	Mean 4.1, s.d. 2.8
Lande, 2012	Mean 26.8, s.d. 3.9, max 35	Male factor (54%), anovulation (18%), unexplained (12%), bilateral tubal occlusion (9%), endometriosis (5%), others (2%)	Mean 2.4 years, s.d. 1.1 years, minimum 1 year	Primary	IVF/ICSI (split not given)	Mean 3.1, s.d. 2.9
Troude *et al.*, 2012	Median 32 (IQR 29–35)	Male factor (37%), female factor (32%), both (18%), unexplained (13%)	0–3 years (51%), 4–5 years (31%), >5 years (15%)	1160 (88%) primary infertility	IVF/ICSI (split not given)	1 (35%), 2–4 (55%), >5 (9%)
Wynter, 2013	20–30 (17%), 31–36 (33%), 37+ (50%)	Unexplained (37.9%), female factors (34%), male factors (16%), both (10%), social e.g. no partner (2.9%)	Mean 93.1 months, s.d. 50.8	Primary	IVF/ICSI (split not given)	No information given
Marcus *et al.*, 2016	Majority 30-34 (42%)	Unexplained (39%), male factor (20%), ovulation problems (10%), tubal factor (13%), endometriosis (11%), others	1–6+	No information given	IVF/ICSI (split not given)	Mean 2.6 cycles per patient
Volgsten and Schmidt, 2017	Mean 38.3, s.d. 3.9	Unexplained (43%), female factors (24%), male factors (20%), both (8%), unknown (6%)	Mean 5.1 years, s.d. 3.1 years	No information given	IVF/ICSI (split not given)	2–3 (54%), 1 (38%), ≥4 (8%)
ElMokhallalati, 2019	Mean 33.9, s.d. 4	Male factor, unexplained, tubal factor, ovulatory disorder, more than one cause, others	Median 5.1, IQR 3.9–6.7	Secondary	652, 61.5% IVF/ 408, 38.5% ICSI	Embryo transfer episodes median 2 (IQR 1–3)

[1] This study sample recruited from a larger cohort reported in a previous study.
[2] These characteristics relate to the wider study population of 817 women. This information was not available for the relevant subgroup (n = 475) used in our study.

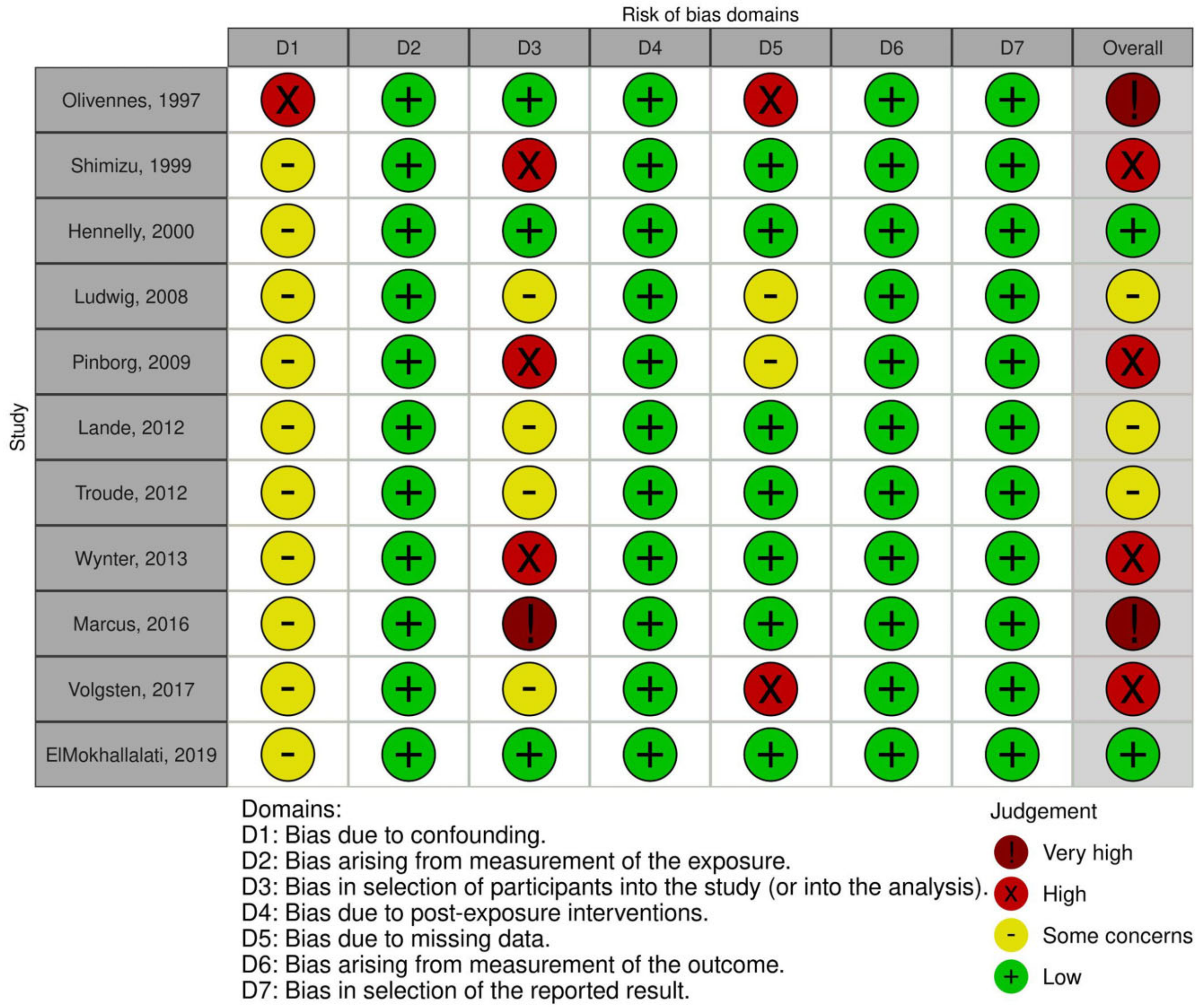

Figure 2. Risk of bias traffic light plot.

measurement of the exposure selection of the reported result was similarly low across all included studies and there were no postexposure interventions.

A range of potential associated factors (e.g. age, cause and duration of subfertility, previous fertility treatment, and gravidity) were considered across the studies. Different covariates were found to be associated with spontaneous conception after ART, including younger age, shorter duration of subfertility, fewer number of treatment cycles prior to first delivery, and specific causes of subfertility. No factors were found to be universally significant across all studies. Maternal age was found to be significantly associated in six studies (Shimizu, 1999; Hennelly, 2000; Ludwig, 2008; Lande, 2012; Troude et al., 2012; ElMokhallalati, 2019). A shorter duration of subfertility, typically <4 years, was also found to be significantly associated with spontaneous conception post ART livebirth in several studies (Hennelly, 2000; Marcus et al., 2016; Volgsten and Schmidt, 2017; ElMokhallalati, 2019). Some studies also reported a significant association with a smaller number of previous IVF, or other treatment, cycles (Pinborg, 2009; Troude et al., 2012; Marcus et al., 2016; ElMokhallalati, 2019), although this was not a consistent finding (Shimizu, 1999; Lande, 2012). Two studies reported a positive association of spontaneous conception post ART livebirth with a short duration of partnership (Ludwig, 2008; Wynter, 2013). Neither of the studies which looked at primary vs secondary subfertility found a significant effect on subsequent natural conception pregnancy or livebirth after ART livebirth (Hennelly, 2000; Troude et al., 2012). One study considered the effect of gravidity of women, but this was reported as non-significant and limited by the size of this subgroup (Shimizu, 1999).

Considering the cause of subfertility, there was also a mixed picture across the included studies. A small, early study did not find any cause or diagnosis of subfertility to be an associated factor with the proportion of women having a natural conception pregnancy after IVF livebirth (Shimizu, 1999). However, unexplained subfertility was identified as an associated factor by four studies (Hennelly, 2000; Troude et al., 2012; Wynter, 2013; Marcus et al., 2016). In addition, Hennelly et al. reported finding that women with endometriosis were significantly more likely to conceive subsequently without treatment and Marcus et al. reported a significantly positive association with ovulation dysfunction. Conversely, tubal factor was a negatively associated factor in two studies (Hennelly, 2000; Pinborg, 2009). Lande et al. also found low levels of spontaneous conception among women who had bilateral tubal occlusion on hysterosalpingography.

Troude et al. reported that male causes, in general, were significantly less likely to result in spontaneous conception, a finding supported by the significant negative association between spontaneous conception and use of ICSI, reported by others (Hennelly, 2000; ElMokhallalati, 2019). Higher natural conception pregnancies were also seen with conventional IVF as opposed to ICSI by Lande *et al.*, although this was not statistically significant ($P = 0.07$). The single study that solely considered women having ICSI (Ludwig, 2008) did not show a lower proportion of natural conception pregnancy compared with the other studies. Lande *et al.* also reported a strong correlation with numbers of motile sperm and spontaneous conception, finding that couples with a very low motile sperm count <0.5 million/ml were less likely to conceive spontaneously, and 21/22 of the couples who conceived spontaneously in their sample had >2 million motile sperm. Ludwig (2008) further reported an association with ejaculatory sperm as compared to testicular or epididymal extraction.

Meta-analysis

Given the significant heterogeneity between studies, a random-effects meta-analysis was used to produce a pooled effect estimate of the incidence of natural conception pregnancy after ART livebirth of 0.20 (95% CI, 0.17–0.22) (Fig. 3). A large degree of heterogeneity was confirmed with an I^2 statistic of 84.6%. The meta-analysis was then stratified by outcome measure; seven studies ($n = 2622$) used natural conception pregnancy; and four studies ($n = 2681$) used spontaneous livebirth. The pooled estimate for livebirths was lower [0.18 (0.14–0.22)] compared with that for natural conception pregnancies [0.20 (0.17–0.24)] as expected, but not statistically significantly so. The corresponding Forest plot is included in Supplementary Fig. S1. The effect of the type of ART (IVF only, ICSI only, or mixed studies) was also considered (Supplementary Fig. S2). The two older IVF-only studies had a lower pooled estimate (0.13 (95% CI, 0.10–0.17)) compared to the eight mixed studies ((0.21 (95% CI, 0.18–0.25)) and the sole ICSI-only study (0.20 (95% CI, 0.17–0.23)). Finally, the effect of the maximum length of follow-up (<5, 5–10, and >10 years) was considered (Supplementary Fig. S3). The pooled estimate for the eight studies which had maximum follow-up periods of 5–10 years remained unchanged at 0.20 (95% CI, 0.18, 0.23), while the two studies which had the longest follow-up periods had the smallest pooled estimate of (0.14 (95% CI, 0.12–0.16)), and single study with a maximum follow-up period of <2 years produced a proportion of 0.33 (95% CI, 0.25–0.41). When data were extracted at 2- and 3-year follow-up periods, the pooled estimates were 0.16 (95% CI, 0.10–0.22) and 0.18 (95% CI, 0.13–0.23), respectively (see Supplementary Figs. S4 and S5). Exclusion of the single cross-sectional study (Marcus *et al.*, 2016) similarly did not significantly impact the overall pooled estimate. Restricting the meta-analysis still further to the five studies not identified at high risk of bias (see Fig. 2), lowered the pooled estimate to 0.18 (95% CI, 0.15–0.21)).

Discussion

To our knowledge, this is the first systematic review and meta-analysis of the evidence on the rate of natural conception pregnancy after ART livebirth. The finding that natural conception pregnancy occurs in one in five women after having a baby via ART contradicts the media message that this is a rare phenomenon. However, given the small number of studies, their individual limitations and differences in population, type of ART, outcome measure, and follow-up, this meta-analysis can only give an indication of the likely incidence based on the current published

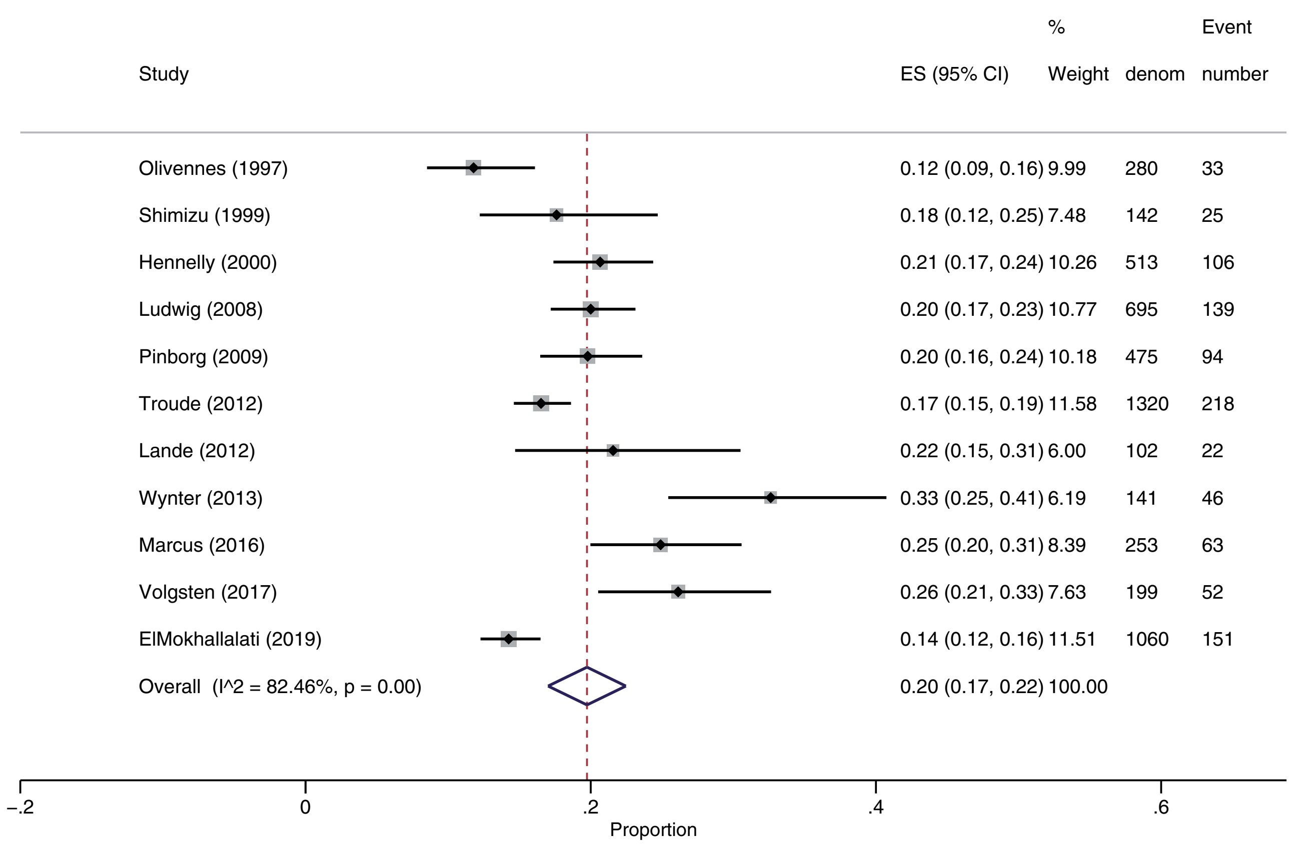

Figure 3. Forest plot of studies of the proportions of spontaneous pregnancies after livebirth via ART. Abbreviations: ES, effect size; event number, number of women having subsequent spontaneous pregnancy/livebirth.

evidence. Despite significant limitations and heterogeneity between the included studies, the pooled estimate was robust when stratifying by the type of ART and outcome measure. Furthermore, using the eight studies for which it was possible to extract data at 3-year follow-up suggested that natural conception pregnancy may occur in 18% of women in the first 3 years after having a baby via ART.

Increasing accessibility to ART, reflecting not just availability but cultural acceptability and affordability, and its use for a broader range of subfertility causes, unexplained subfertility, and other non-subfertility indications, may result in an increase in the incidence of natural conception pregnancy after ART livebirth. While it is recognized that information for couples contemplating ART should include an estimate of their chance of natural conception pregnancy (European Society of Human Reproduction and Embryology (ESHRE) Capri Workshop Group, 2013), it is perhaps less appreciated that this should be reassessed and communicated to couples presenting for further fertility treatment after successful ART. There is unanimous agreement across the studies that the rates of natural conception pregnancy after successful IVF/ICSI are practically helpful and should be used to counsel women and couples having had and considering further IVF/ICSI. Two included studies (Ludwig, 2008; Marcus *et al.*, 2016) assert that couples having ART think they cannot conceive spontaneously, and this view is supported by recent qualitative evidence (Thwaites, 2022) exploring the lack of contraception use in this group.

The potential for fertility treatment to improve spontaneous fertility has been suggested as early as 1979 (Bernstein, 1979; Haney, 1988); however, it has not been rigorously investigated. It is biologically plausible that ovarian stimulation from IVF cycles may improve ovarian function in a similar mechanism to the surgical technique ovarian drilling. Other commonly cited hypotheses include pregnancy induced endocrinological changes e.g. endometriosis regression during gestation (Shimizu, 1999; Wynter, 2013) and stress reduction. Certainly, the importance of psychological factors on fertility is well recognized and widely accepted. There are studies exploring pregnancy rates on IVF/ICSI waiting lists suggesting that this may be as high as 25% at one year for some groups and highest for those with unexplained subfertility (Eijkemans *et al.*, 2008), perhaps in part due to the relief of being on the pathway to treatment. However, two studies included in this review showed higher proportions of natural conception pregnancy in women who had had unsuccessful fertility treatment and who therefore did not experience a removal of stress to conceive (Troude *et al.*, 2012; Marcus *et al.*, 2016), although this is not a consistent finding in the context of the wider literature on the incidence of natural conception pregnancy after unsuccessful IVF.

However, when attempting to interpret, compare, and synthesize these studies, it is important to consider wider underlying differences between them, potential confounding factors, and their significant limitations. The generalizability of study findings is limited based on time and location as the demand for and access to ART is highly dependent on context, culture, and cost (Chambers, 2009). Pregnancy rates resulting from IVF have increased dramatically over the last four decades and are now successful in 50% of cycles in women under the age of 35 (Eskew and Jungheim, 2017). This compares with pregnancy rates of 22% in 1995 to 33% in 2003 (Wang and Sauer, 2006). IVF was still a new technique during the recruitment period of the two earliest studies, which were restricted to women with tubal subfertility (Olivennes, 1997) and, predating ICSI, these studies excluded severe male-factor subfertility in their cohorts. This may account for the lower pooled estimate of the incidence of natural conception pregnancy after ART livebirth seen in the IVF-only studies. The indication for and timings of ART are potential confounding factors. However, the mixed ART studies and ICSI-only study had the same pooled estimates as the overall figure of 0.20.

The Australian study reported the highest estimated proportion of natural conception pregnancy after ART livebirth (33%), which may be partially attributable to the accessibility of ART there at a relatively low cost (Wynter, 2013). The second highest proportion was seen in the Swedish study (Volgsten and Schmidt, 2017), which similarly offers government-subsidized ART and treatment across the private and public sectors. Denmark has the highest utilization of ART per inhabitant in Europe (Pinborg, 2009) with its public health service funding IUI and three fresh ART cycles during 2000–2001. However, this study recruited from tertiary centres, which may have a population with more severe reproductive disorders compared to other studies. Israel is perhaps the most ‘cost-free’ environment with unlimited IVF treatments given for up to two children until age 45 years at the time of the study (Birenbaum-Carmeli and Dirnfeld, 2008). However, Lande *et al.* use the outcome measure of livebirths, which may account for the relatively lower proportion (22%) compared to the Australian study. Diagnostic and protocol differences may also account for differences in results; for example, in Australia, diagnostic laparoscopy is no longer first-line investigation and therefore couples with an ‘unexplained’ cause may include hidden endometriosis, whereas women in the older Japanese study had diagnostic laparoscopy (Shimizu, 1999).

Other potential confounding factors include maternal age, shorter duration of subfertility, fewer number of treatment cycles prior to first delivery, and specific causes of subfertility. However, these were not consistently defined nor categorized across the studies. Maternal age, known to be the strong predictor of both natural conception and IVF success (European Society of Human Reproduction and Embryology (ESHRE) Capri Workshop Group, 2005), was not found to be significantly associated with the incidence of natural conception pregnancies in two studies (Wynter, 2013; Marcus *et al.*, 2016) suggesting that they may have been underpowered for this analysis. There was a more mixed picture reported regarding associations with causes of subfertility with the most consistent evidence (in four studies) identifying unexplained fertility as being associated with a higher incidence of subsequent natural conception pregnancy. This was also suggested in a systematic review into the rate of natural conception in women over 35 with subfertility, which found that natural conception is still clinically relevant in this group and significantly higher with unexplained subfertility compared to other diagnoses (Chua, 2020). However, the numbers of women in subgroups of interest were frequently small and larger data-linkage studies are needed to establish associated factors.

The risk of bias assessment (Fig. 2) also revealed that some studies were at high risk of selection bias, with women who have had a natural conception pregnancy after a livebirth via ART potentially more likely to participate, leading to overestimation of the incidence of natural conception pregnancy. Pinborg *et al.*, using linkage to the national birth register, reported a 5% difference in response rate between those who did and did not give birth (Pinborg, 2009). Similarly, the study with a comparator group of women who had first infants via natural conception found that loss to follow-up was significantly more common in this group compared to the group of women who had a first infant conceived by ART (Wynter, 2013), introducing bias. The largest study included in this review (Troude *et al.*, 2012) had a population in which 97% had had successful IVF and 3% had births following other fertility treatments, including ovarian stimulation, surgery, oocyte donation, and ICSI, but mainly artificial IUI with partner or donor sperm which is a limitation of the study and which is reflected in the concerns under the selection bias domain. The risk of selection bias also applies to the single cross-sectional survey (Marcus *et al.*, 2016). This study recruited participants via a website, founded by the lead author, which offers free information on infertility (Marcus, 2022). A response rate could therefore not be calculated. By contrast, the single data-linked study was not limited by loss to follow-up as it used the assisted reproduction unit database and national maternity database (ElMokhallalati, 2019). A good quality national database was also used in part by (Pinborg *et al.*, 2009). However, both studies could be subject to underestimation as they did not have information on births that occurred outside of Scotland and Denmark respectively.

Other concerns in the risk of bias assessment related to missing data. As we analysed subgroups from prospective studies as a nested retrospective cohort, it was not always possible to calculate response rates or to be sure of the representativeness of the sample. Longitudinal designs also incur conflict between allowing long enough follow-up time to allow for pregnancies to occur and increased risk of loss to follow-up. Both response and dropout rates were highly variable and often not quoted nor derivable. While we may expect longer follow-up periods to correlate with greater loss to follow-up, this trend was not clearly shown. The two oldest studies (Olivennes, 1997; Shimizu, 1999) had extremely low loss to follow-up but were single-centre, relatively small studies with a selective population. Ludwig *et al.* assert that the response rate seen in their study (56%) is what can be realistically expected after five years and performed a sensitivity analysis reporting that the proportion of natural conception pregnancy of 20% or 1 in 5 would be 12.5% or 1 in 8 if all the women lost to follow-up failed to conceive again (Ludwig, 2008).

Restricting the meta-analysis to the five studies not identified as having high risk of bias lowered the pooled estimate of the incidence of natural conception pregnancy after ART livebirth only slightly to 0.18 (95% CI, 0.15–0.21) (Supplementary Figure S6). This subgroup included the four largest studies and the most recent study. However, there is potential publication bias with studies finding that natural conception pregnancy does not occur commonly after a livebirth via assisted conception being less likely to be published.

Four studies reported natural conception livebirths, which underestimates the incidence of natural conception pregnancy by excluding non-birth outcomes (e.g., miscarriage, termination). Other potential reasons why this is likely an underestimate include the lack of consideration of pregnancy intention and contraception use in the included studies. Two studies stopped follow-up if natural conception pregnancy was achieved (Shimizu, 1999; ElMokhallalati, 2019) and two excluded any subsequent natural conception pregnancies from their analysis (Hennelly, 2000; Marcus *et al.*, 2016) The remainder of studies did not give information on the incidence or analysis of multiple sequential natural conception pregnancies, which was largely overlooked.

The longitudinal studies also variably established and excluded women on the basis of a new male partner. Three studies excluded a small proportion of their cohort on this basis (Ludwig, 2008; Lande, 2012; Troude *et al.*, 2012). One study established that the majority (92.8%) were still living with the same partner but did not exclude those who were not, potentially overestimating the proportion of natural conception pregnancy especially if the cause was male-factor subfertility (Volgsten and Schmidt, 2017). Pinborg *et al.* reported that 16 women who had natural conception pregnancies had changed partners but did not report how they were distributed across the groups who had conceived spontaneously after a previous ART delivery and those who had not. The remaining longitudinal studies did not consider partnership status.

Finally, six studies did not consider contraception nor whether the subsequent pregnancy after ART livebirth was planned (Olivennes, 1997; Hennelly, 2000; Pinborg, 2009; Troude *et al.*, 2012; Volgsten and Schmidt, 2017; ElMokhallalati, 2019). Some studies simply excluded women based on any contraception use (Shimizu, 1999; Ludwig, 2008; Lande, 2012; Marcus *et al.*, 2016). Moreover, contraception status was often implied and/or grouped together with reasons for the couple not having sex again, i.e. couple separation, divorce, or death. One study did ask 'was this pregnancy unexpected, at the time you wanted, or after some months of trying?' (Wynter, 2013) and more than half of subsequent natural conception pregnancies after ART livebirth were reported as 'unexpected'. However, no data in this study were collected regarding the preferred spacing of children, breastfeeding, or contraception use. Studies that assume all fertility patients try to conceive and do not use contraception underestimate the true incidence of natural conception pregnancy. Moreover, a binary measure of contraception use at a single time point is unhelpfully simplistic since contraception use can be discontinued, intermittent, or subject to a wide range of method-dependent and user-dependent variables. The reliability of self-reported contraception use itself may be lower as it is prone to bias (Smith, 2018). Given failure rates with perfect use are also significant and method-dependent, studies that simply exclude women who use contraception also miss natural conception pregnancies in this group.

Future studies looking at the incidence and rates of natural conception pregnancy after ART are well aligned with the recently published international consensus development study into priorities for infertility research (Duffy *et al.*, 2021). Large data-linked studies are ideally needed to provide more accurate estimates and analysis of associated factors and trends over time. These should include consideration of changes in partner, contraception use, pregnancy planning, and interpregnancy intervals. However, the existence and extent of national health data registers are highly variable. Two studies included in this review (Pinborg, 2009; ElMokhallalati, 2019) were able to use linkage to the Danish medical birth register and Scottish national maternity database respectively. By contrast, a recent review of UK national population-level indicators and core data sources has shown that measures of ART are currently only collected routinely in the fertility regulator (HFEA) database not as part of the maternity services data set and pregnancy intention is not recorded in any routine dataset (Schoenaker *et al.*, 2022). Routine inclusion of IVF status and multi-question, psychometrically validated measures of pregnancy intention (e.g. the London Measure of Unplanned Pregnancy (Barrett, 2022)) alongside national birth data would facilitate future studies into the use of natural conception pregnancy after ART and increase the utility of this measure for tailored counselling in clinical settings.

In conclusion, this first systematic review and meta-analysis of natural conception pregnancy after ART livebirth suggest that this is far from rare, affecting one in five women after having a baby via IVF or ICSI. This is in contrast with views commonly expressed in the media and by women with this reproductive history that it is an unlikely, surprising, or 'miracle' event. Despite significant limitations and heterogeneity between the included studies, the pooled estimate was robust when stratifying by type of ART and outcome measure. In addition, the available data suggest that natural conception pregnancy may occur in 18% of women in the first 3 years after having a baby via ART. These pooled estimates are likely to be underestimates as some studies reported on spontaneous livebirths (i.e. excluding non-birth outcomes), some did not include births that occurred outside of the study region or centre, and no studies gave due consideration to contraception use, plannedness of pregnancies, interpregnancy intervals, change in partner, nor serial natural conception pregnancies in the same woman. Moreover, the increasing trend in accessibility and use of IVF, including growing subgroups of women who use IVF primarily for reasons other than subfertility, may cause the incidence of natural conception pregnancy after ART livebirth to increase further. National, data-linked studies are needed to provide more accurate estimates of this and analysis of associated factors and trends over time.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

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Authors' roles

A.T.: study design, data collection, data analysis, and writing of the manuscript. J.H.: substantial contributions to the design, data analysis and interpretation, and critical revision of the manuscript. G.B. and J.S.: substantial contributions to the design, data interpretation, and critical revision of the manuscript. All authors: final approval of the version to be published and agreement to be accountable for aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest

No authors have any conflicts of interest.

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