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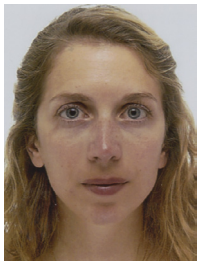
REVIEW

Pregnancy following diagnosis of premature ovarian insufficiency: a systematic review



BIOGRAPHY

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KEY MESSAGE

The diagnosis of premature ovarian insufficiency (POI) is frequently devastating for a previously healthy young woman, carrying with it the likelihood of permanent sterility. Even though pregnancies without donor egg treatment are unusual, however, they do occur, and clinicians should not be too hasty to label young women with POI as beyond hope.

ABSTRACT

The aim of this review is to report the occurrence of pregnancies in women with premature ovarian insufficiency (POI), naturally or with different treatments (hormonal replacement therapy, IVF, in-vitro maturation and stem cell therapy). This study involved an exhaustive search of the electronic databases *MEDLINE*, *PubMed* and *Embase* covering the period January 2000 to January 2018. A combination of Medical Subject Heading and text words was used to generate a subset of citations, including studies involving POI ('premature menopause' or 'premature ovarian failure' or 'POI' or 'hypergonadotrophic amenorrhoea'). This subset of citations was then combined with 'AND' to the Medical Subject Heading term 'pregnancy'. Fifteen studies were included in this review. Two randomized controlled trials, two observational studies, and 11 interventional studies reporting cases of pregnancy in women with POI were included. This review reports pregnancy rates across studies ranging from 2.2% to 14.2%. Mean age in patients who achieved a pregnancy was 30 years, highlighting that oocyte quality in these patients is likely unaffected. No treatment has thus far shown its superiority in improving fertility in women with POI. Recent advances in options such as in-vitro maturation and stem-cell therapy, however, are likely to be the future of treatment and may generate new hope for these patients.

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KEYWORDS

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Live birth
Pregnancy
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INTRODUCTION

Premature ovarian insufficiency (POI) has been defined by the European Society of Human Reproduction and Embryology as encompassing three criteria: the presence of primary or secondary amenorrhoea for more than 4 months, onset before the age of 40 years and an FSH level greater than 25 mIU/ml (as determined by two measurements obtained at least 4 weeks apart) (*Baber, 2014; Webber et al., 2016*). Anti-Müllerian hormone (AMH) is not used for the diagnosis. This biomarker, however, reflects the size of the primordial follicle pool and, therefore, patients affected by POI will be expected to have low serum AMH (*Visser et al., 2012*). The term 'premature ovarian insufficiency' is preferred over 'premature menopause' because it does not imply a total cessation of ovarian activity. It is relatively rare, with an occurrence of one in 100 women before the age of 40 years, one in 1000 women before the age of 30 years and one in 10,000 before the age of 20 years (*Fenton, 2015*).

Three main mechanisms have been suggested as potential causes of POI: early follicular depletion, a blocking of follicular maturation or a destruction of the oocyte pool (*Koninckx and Brossen, 1977*). Another possible underlying mechanism is resistant ovarian syndrome first described in 1969, which encompasses secondary amenorrhoea, high FSH levels, an age-compatible antral follicle count (AFC) by sonography or the presence of follicles at biopsy and an age-appropriate AMH (*Jones and De Moraes-Ruehsen, 1969*). The physiology implies the inability of multiple antral follicles to respond to endogenous or exogenous FSH, and the diagnosis has in the past been made histologically from an ovarian biopsy, although this practice has largely been discontinued owing to surgical risk and absence of any evidence-based treatment for the condition (*Khastgir et al., 1994; Goswami and Conway, 2005; Webber et al., 2016*).

The possible causes of POI can be divided into genetic, iatrogenic, autoimmune, metabolic, infectious or environmental (*Hernandez-Angeles and Castelo-Branco, 2016; Overbeek et al., 2017; Vabre et al., 2017*). The cause of POI, however, remains mostly unknown. Estimations of the prevalence of idiopathic POI vary between 50 and 90% of cases (*Maclaran and Panay, 2011; Bricaire et al., 2013; Webber et al., 2016*). Genetic causes are mostly caused by X chromosome abnormalities, including Turner syndrome (4–5%), triple X syndrome (1–4%), fragile X premutations (3–15%) and translocations involving the X chromosome. Recently, several genes have been implicated in the involvement of the pathogenesis of POI, including *NOBOX*, *FOXO3*, *GDF9* and *BPM15* variants (*Joop, 2016; Moriwaki et al., 2017; Rossetti et al., 2017*). Iatrogenic causes mainly stem from oncological treatments, such as chemotherapy, radiotherapy or extensive surgery; on occasion, they may follow surgical treatment of ovarian endometriosis or benign ovarian cystic disease (*Iwase et al., 2014*). Autoimmune diseases are also frequently observed in patients with POI (hypothyroidism in 20%, adrenal insufficiency in 10–20% and other autoimmune disorders such as myasthenia, systematic lupus erythematosus, rheumatoid arthritis and congenital thymic aplasia have been described). In some cases, antibodies against the ovaries can also be found (*Irvine, 1969; Collins et al., 2017*), although currently available methods of detection of anti-ovarian antibodies are imprecise (*Wheatcroft et al., 1997; Novosad et al., 2003*). Metabolic disorders such as 17-hydroxylase deficiency and galactosemia are also associated with POI, as are a number of infectious diseases, including paramyxovirus (mumps), human immunodeficiency virus or pelvic inflammatory disease (*Goswami and Conway, 2005*). Recent studies have also implicated environmental pollutants as a cause of POI (*Vabre et al., 2017*).

Pregnancy is uncommon in this population, and egg donation is often the only solution for subsequent infertility. In 5–10% of cases of POI, however, pregnancy can occur naturally, with hormone replacement therapy (HRT), IVF, or, more recently, in-vitro maturation (IVM) or with stem cell therapy (*Van Kasteren and Schoemaker, 1999*). Numerous case reports also support this statement (**TABLE 1**) (*Check et al., 2000; 2004; 2009; Nawroth et al., 2000; Zargar et al., 2000; Takahashi et al., 2001; Fernandes, 2002; Hershlag and Schuster 2002; Chao et al., 2003; Eldeen and Fawzi, 2003; Muller et al., 2003; Patel et al., 2003; Aslam et al., 2004; Menezo et al., 2004; Vital-Reyes et al., 2004; Corrigan et al., 2005; Check and Katsoff, 2006; 2008; Vandborg and Lauszus, 2006; Liza et al., 2008; Dragojevic-Dikic et al., 2009; Genazzani, 2009; Neves-e-Castro, 2009; Selvaraj et al., 2010; Chen and Chen, 2011; Ebrahimi et al., 2011, Ferrau et al., 2011; Laway et al., 2011; Tartagni et al., 2011; Ghazeeri and Awwad, 2012; Grynberg et al., 2013; Maruyama et al., 2013; Soave et al., 2013; Tsuji et al., 2013; Rogenhofer et al., 2014; Warenik-Szymankiewicz and Slopien 2014; Roth and Alvero, 2014; Li et al., 2016*).

To date, no clinical test can determine the potential for conception in patients with POI. As a result, it may be clinically prudent not to be too premature in diagnosing absolute infertility in women diagnosed with POI, particularly in patients aged under 30 years. This will allow patients the time and opportunity to have a chance to conceive with their own oocyte if they are not ready to move forward to egg donation.

The diagnosis of POI is frequently devastating for a previously healthy young woman, carrying with it the likelihood of permanent sterility, consequences of early onset hypo-oestrogenism and the stigma of being labelled as menopausal. Many patients diagnosed with POI find it difficult to accept their loss of fertility and will request treatment with superovulatory agents despite being appraised of their very low chances of success. Some patients with POI find it easier to move on to oocyte donation once such treatments have been tried and found unhelpful.

The occurrence of pregnancy in patients with a diagnosis of POI was last systematically reviewed in 1999 (*Van Kasteren and Schoemaker, 1999*). The aim of this review is to report on pregnancies known to have been achieved by women diagnosed with POI according to the European Society of Human Reproduction and Embryology diagnostic criteria. The body of published research is extensive; hence, discussion of the studies will be segregated according to their design.

SYSTEMATIC REVIEW

Literature search strategy

The present study involved an exhaustive search of the *MEDLINE*, *PubMed* and

TABLE 1 CASE REPORTS

Interventions	Number of studies	Number of pregnant patients
No treatment	7	8
HRT (oestrogen + progesterone)[a]	12	12
HRT + triggering	1	1
HRT + recombinant FSH	2	2
HRT + HMG	1	1
HRT + recombinant FSH + HMG[b]	1	1
HRT (oestrogen + progesterone or tamoxifen) after autologous stem-cell transplantation	1	3
OCP	1	2
OCP + recombinant FSH	1	1
Oestrogens	2	3
Oestrogens + GnRH agonist + HMG	1	1
Oestrogens + recombinant FSH (IVF/ICSI)	2	2
Oestrogens + HMG + recombinant FSH	1	1
Oestradiol + FSH + prednisolone	1	0 (= surrogacy with eggs of patient with POI)[c]
Recombinant FSH	1	1
Chinese herbal	1	1
Azathioprine	1	1
Antagonist	1	1
IVM[b]	2	2

[a] Including two patients with Resistant Ovarian Syndrome.

[b] Patients with Resistant Ovarian Syndrome.

[c] Use of a surrogate after four implantation failures in the patient with premature ovarian insufficiency.

GnRH, gonadotrophin releasing hormone; HMG, human menopausal gonadotrophin; HRT, hormone replacement therapy; ICSI, intracytoplasmic sperm injection; IVM, invitro-maturation; OCP, oral contraceptive pill; POI, premature ovarian insufficiency.

Embase electronic databases covering the period January 2000 to January 2018. A combination of Medical Subject Heading and text words were used to generate a subset of citations, including studies involving POI ('premature menopause' or 'premature ovarian failure' or 'POI' or 'hypergonadotrophic amenorrhoea'). This subset of citations was then combined with 'AND' to the Medical Subject Heading term 'pregnancy'.

Eligibility criteria

This review incorporates all articles about pregnancy in patients diagnosed with POI, including randomized controlled trials (RCTs), observational studies and interventional studies published since the last review of this topic was conducted in 1999 (*Van Kasteren and Schoemaker, 1999*).

Exclusion criteria

Studies published in a language other than English or French and, those regarding oocyte donation pregnancies, POI without pregnancy, pregnancy after ovarian transplant from another patient and pregnancy after ovarian transplant from the patient's own ovaries before POI, were all excluded from this review.

Study selection

Titles and abstracts of the identified studies were scrutinized, and irrelevant studies removed. The full text of potentially relevant studies was retrieved, assessed and, if relevant, included in the study.

Two thousand and fifty-three records met the search criterion, 1838 records were excluded based on title, abstracts, or both. Two-hundred and fifteen full-text articles were assessed for eligibility, 200 were irrelevant for the study (no pregnancy, egg donation, ovarian transplant from another patient, ovarian transplant from the patient before POI, in languages other than French or English or case reports), 37 were only case reports and three were Letters to the Editor. Finally, 15 studies were included in this review. The study selection is presented in FIGURE 1.

Reported pregnancy rates in patients with premature ovarian insufficiency

We found two RCTs, two observational studies and 11 interventional studies about cases of pregnancy in women with POI.

Quality of included studies

The quality of evidence in the two RCTs was rated in accordance with the GRADE working group and were both judged as moderate (*Robles et al., 2013*). The interventional and observational studies were of low-quality evidence.

RESULTS

Randomized controlled trials

The RCTs are presented in TABLE 2. In the RCT conducted by *Tartagni et al. (2007)*, ovarian stimulation was thought to be more efficient after reducing circulating FSH by pre-treatment with oestrogen. Fifty patients with POI were included, of whom 20 patients also had autoimmune disorders (nine with anti-thyroglobulin antibody, five with anti-microsomal antibody, five with anti-adrenocortical antibody and one with anti-ovarian antibody). Nine patients had a family history of POI. No other causes were found. Participants were split into two randomly assigned groups of 25 patient. Group one received treatment with ethinyl oestradiol before stimulation and group two received placebo. Concentrations of FSH in group one decreased from 68.3 +/− 20.0 IU/l (mean +/− SD) to 15.6 +/− 5.3 IU/l. The ovulation rate in group one was 32%, whereas, in group two, it was 16%. No pregnancies were reported in group two, whereas the pregnancy rate in group one was 16% (four patients were able to conceive, and all pregnancies resulted in a live birth). The mean pregnancy rate for the entire cohort was 8% (*Tartagni et al., 2007*). The study, however, was underpowered for any conclusions to be made on pregnancy outcomes.

In the RCT conducted by *Badawy et al. (2007)*, the hypothesis was that idiopathic POI may be caused by autoimmune factors. Each of the 58 patients with idiopathic POI who participated were randomly allocated to receive either gonadotrophin-releasing hormone agonists (GnRHa) and gonadotrophin with the addition of corticosteroids (n =29)

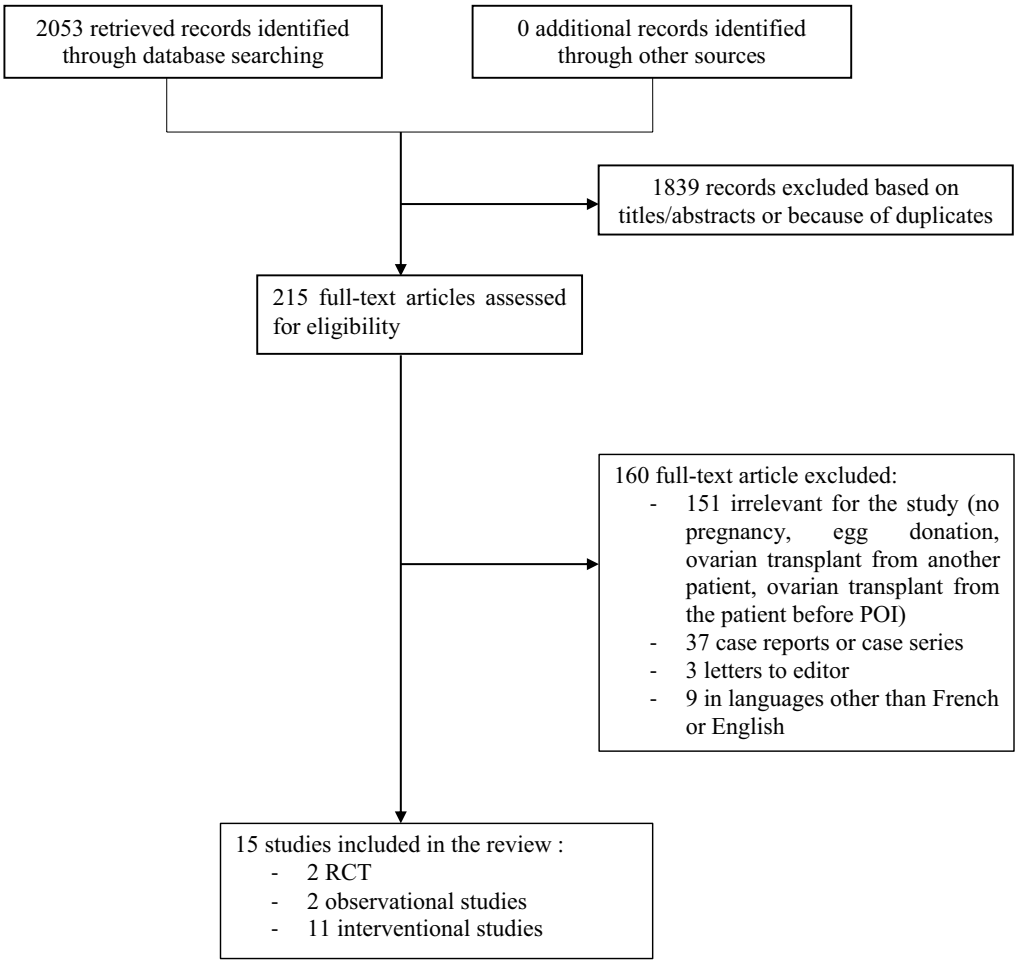

FIGURE 1 Identification and selection process.

or GnRHa and gonadotrophin with the addition of placebo (n = 29). Ovulation rates were significantly better in the group treated with dexamethasone (20.7%, versus 10.3% in the placebo group), and two pregnancies were achieved in the treatment group (live birth rate was not reported), whereas no pregnancies occurred in the placebo group. The final pregnancy rate for the study was 3.4%. Nonetheless, regarding the efficacy of the treatment, with only two pregnancies in the treatment group and no pregnancies in the placebo group, the study was, here again, underpowered for any conclusions to be made on pregnancy outcomes (*Badawy et al., 2007*).

Uncontrolled interventional studies

The uncontrolled interventional studies are presented in TABLE 3. In a

TABLE 2 CHARACTERISTICS AND RESULTS OF THE REVIEWED RANDOMIZED CONTROLLED TRIALS

Reference	Number of patients	Design	Characteristics of the population	Intervention	Pregnancy rate (%) (ratio)	Quality of evidence
Tartagni et al. (2007)	50	RCT	Age (years): 32.9 (3.9) FSH (IU/l): 68.32 (20.01) Oestradiol (pg/ml): 13.2 (4.8) Amenorrhoea (months): 16.9 (9.05) Age (y): 32.5 (4.8) FSH (IU/L): 67.8 (19.5) E2 (pg/ml): 13.9 (4.25) Amenorrhea (months): 16.6 (9.99)	Ethinyl-oestradiol 0.05/ 8 h for 14 days + recombinant -β-FSH (n = 25) Placebo/ 8 h for 14 days + recombinant β-FSH (n = 25)	16 (4/25)[a] 0 (0/25)	Moderate
Badawy et al. (2007)	58	RCT	Age (years): 28.2 (4.32) FSH (IU/l): 54.1 (3.1) Duration of POF (years): 5.2 (3.71) Age (years): 26.2 (5.32) FSH (IU/l): 48.1 (3.7) Duration of POF (years): 6.3 (3.82)	Triptorelin 3.75 mg + dexamethasone 6 mg/ day for 28 days + HMG 300 UI/day for 10 days (n = 29) Triptorelin 3.75 mg + placebo/d for 28 days + HMG 300 UI/day for 10 days (n = 29)	6.9 (2/29)[a] 0 (0/29)	Moderate

[a] Not statistically significant.

Results are given in mean (SD).

HMG, human menopausal gonadotrophin; POF, premature ovarian failure; RCT, randomized controlled trial.

TABLE 3 INTERVENTIONAL AND OBSERVATIONAL STUDIES

Reference	Number of patients	Characteristics of the population	Number of pregnancies (%)	Follow-up (years)	Intervention
Interventional studies					
Zhang et al. (2007)	138	Age (years): 30.36 (4.05) FSH (IU/l): 74.42 (27.67) Oestradiol (pg/ml): 28.6 (35.44)	3 (2.2)	3	Oestrogen 1–2 mg/day/21 days + progesterone intramuscular 20 mg/day/5 days +/– corticosteroids +/– ovarian stimulation.
Meden-Vrtovec et al. (2011)	70	Age (years): 32.5 (5.71) Amenorrhoea (years): 1–15	3 (4.3)	5	Oestradiol valerate 2 mg/day + norgestrel 0.5 mg/day.
Chen et al. (2016)	44	Age (years): 31.3 (27–38) FSH (IU/l): 93.69 (51.87–205) Oestradiol (pg/ml): 36.78 (5–45.58)	3 (6.8)	4	Oestradiol valerate 4 mg/day +/–oral dydrogesterone 10 mg/day +/ 10,000 IU HCG, ICSI.
Bachelot et al. (2016)	507	Age (years): 31.6 (6.4)	18 (3.6)	4.1[a]	HRT.
Check et al. (2016)	5	?	3 (60)	–	Ethinyl-oestradiol + IVF.
Mamas and Mamas (2009)	5	Age (years): 37 (1.9) FSH (IU/l): 65.8 (34.1) Amenorrhoea (months): 8.4 (3.9) Oestradiol (pg/ml): 26.4 (6.7)	5 (100)	1	DHEA (25, 50 or 75 mg/day)[b] +/– IUI.
Suzuki et al. (2015)	37	Age (years): 37.6 (4.6)	3 (8.1)	–	IVA, auto-transplantation, conjugated oestrogen 0.625–1.875 mg, 150–300 IU recombinant FSH, 0.25 mg cetrolix, 10,000 HCG, ICSI.
Zhai et al. (2016)	14	Age (years): 29.2 FSH (IU/l): 94.5 Amenorrhoea (years): 3.8	1 (7.1)	1	IVA +/– oestradiol valerate 3 mg/day/21 days + dydrogesterone 20 mg/day/5 days or GnRH agonist 0.1 mg/day +/– 300–450 IU HMG.
Ding et al. (2018)	14	Age (years): 30.5 (3.8) FSH (IU/l): 51.8 (6.3)	2 (14.2)	–	Stem-cell ovarian transplant + conjugated oestrogen 0.625 mg/day/25 days + medroxyprogesterone acetate 10 mg/day/10 days.
Observational studies					
Letur et al. (2004)	518[c]	?	17 (3.3)	11.5[a]	HRT or no treatment
van Erven et al. (2017)	21[d]	Age (years): 33	9 (42.9)	2	HRT or no treatment.

[a] Mean.

[b] Dose increased according to ovarian response.

[c] Including premature ovarian insufficiency and occult premature ovarian insufficiency.

[d] Trying to conceive.

Results are given in mean (SD) or median (range) for the characteristics of the population.

DHEA, dehydroepiandrosterone; GnRH, gonadotrophin releasing hormone; HMG, human menopausal gonadotrophin; HRT, hormone replacement therapy; IVA, in-vitro activation; IUI, intrauterine insemination; ICSI, intracytoplasmic sperm injection.

retrospective cohort of 138 infertile Chinese women with POI (*Zhang et al., 2007*), all patients received HRT. Of the 138 participants, 115 had idiopathic POI, 11 had an abnormal karyotype, 10 had iatrogenic POI and two had autoimmune disorders. Hormone concentrations were measured at baseline and after 3 months of cyclical HRT. Corticosteroids may have been added in some cases, as described in their treatment strategy. If FSH concentrations fell below 40 UI/l, ovarian stimulation was carried out. Three patients out of the 138 conceived, giving a pregnancy rate of 2.2%. Two participants conceived while taking the hormone replacement therapy and the third one with the ovarian stimulation after HRT.

In an observational uncontrolled retrospective study by *Meden-Vrtovec et al. (2011)*, 70 patients with POI received HRT. Of the participants, 23 patients had idiopathic POI, 30 had iatrogenic POI and 17 had an abnormal karyotype. Three out of the 23 idiopathic patients with POI aged 35, 35 and 21 years, respectively, became pregnant (pregnancy rate 13% or 4.3% for the whole cohort) after HRT treatment and delivered healthy babies. One participant had twins.

Forty-four women, with idiopathic POI were described in the retrospective analysis by *Chen et al. (2016)*. All participants were treated with HRT. Twenty women had intermittent follicular development. Among them, seven attempted natural pregnancy and two conceived. One had a miscarriage, and the other one had a healthy child. The other 13 women remained under HRT and, when the diameter of a follicle exceed 14 mm, underwent ovulation induction and egg retrieval. Intracytoplasmic sperm injection was carried out and two women underwent embryo transfer. Only one women, aged 27 years, had a successful pregnancy and delivered a healthy baby (pregnancy rate 6.8%).

In a retrospective cohort study by *Bachelot et al. (2016)*, 507 patients with idiopathic POI were included to track the outcome after resumption of ovarian function defined by the occurrence of a spontaneous pregnancy, resumption of menstrual cycles, or both. All patients were prescribed HRT. One hundred and seventeen patients experienced a resumption of ovarian function (23%) and 18 patients (3.6% of the whole cohort) ultimately conceived (live birth rate was not reported) (*Bachelot*

et al., 2016). This report expanded on a previous study by Bidet et al. (2011) conducted 5 years earlier with a subset of the same cohort, comprising 358 patients in which 15 patients conceived (4.2%), 21 became pregnancy, 16 had live births (one twin birth), four miscarried and one elected to terminate the pregnancy (pregnancy rate 5.9%) achieved. The retrospective design of these studies is their main limitation.

In an abstract, Check et al. (2016) described a prospective observational series, including five women with idiopathic POI who underwent IVF cycles with preceding ethinyl oestradiol treatment; three became pregnant (pregnancy rate 60%). The overall pregnancy rate from the study was 23.5% per transfer (four out of 17), 14.3% per retrieval (four out of 28) and 7.8% per initiated cycle (four out of 51). This abstract has not been published as a peer-reviewed article (Check et al., 2016).

Finally, in a study conducted by Mamas and Mamas (2009), five patients with idiopathic POI underwent dehydroepiandrosterone (DHEA) treatment. All patients in this study conceived, and, at the time of publication, one had given birth to a healthy baby, three had ongoing pregnancies and one had miscarried. The pregnancy rate for this study was theoretically 100% but the small sample size of only five patients prevents us from drawing any meaningful conclusions from this finding.

More recently, some studies have assessed the efficacy of IVM and stem-cell therapy. The cause of the POI was not described in any of these studies. In the prospective observational study by Kawamura et al. (2013), 27 patients with POI underwent a bilateral laparoscopic oophorectomy. Thirteen patients had pre-antral follicles at the histological analysis. In-vitro activation based on Hippo signalling disruption and Akt stimulation was carried out, followed by auto transplantation and ovarian stimulation. Mature oocytes were successfully retrieved in only five patients after auto transplantation and stimulation. All patients underwent oestrogen therapy before stimulation and, when antral follicles were detected, ovarian stimulation was begun. Intracytoplasmic sperm injection was carried out for all patients. Three participants had an embryo transfer, one patient had a biochemical pregnancy and one participant (aged 29 years) had a healthy baby (pregnancy rate 7.4%) (Kawamura et al., 2013). The same cohort was enlarged with 10 new patients in a study conducted by Suzuki et al. (2015). The same protocol was used, resulting in 20 out of the 37 patients having residual follicles, and nine out of those 20 had follicular growth. One live birth was achieved in the new cohort, giving an overall pregnancy rate of 8.1%.

In another observational prospective cohort study conducted by Zhai et al. (2016), 14 women with POI who underwent laparoscopic unilateral oophorectomy were followed. In-vitro activation was conducted using a phosphatase and tensin homologue inhibitor and phosphatidylinositol-3 kinase activator. After 2 days of in-vitro activation, ovarian transplants were replaced beneath the serosa of the fallopian tube and ovarian stimulation followed by oocyte retrieval and intracytoplasmic sperm injection (ICSI) was carried out. Seven patients had residual follicles, and six had follicle development. In these six patients, three had spontaneous follicular development with or without HRT, three had induced follicular development either with GnRH agonist followed by human menopausal gonadotrophin (HMG) or HMG treatment with or without HRT pre-treatment. Only one patient (35 years old) delivered a healthy baby (pregnancy rate 7.1%) (Zhai et al., 2016).

Finally, in the most recent interventional study, Ding et al. (2018) used ovarian stem cell injection. Fourteen patients with idiopathic POI were randomly assigned to receive either ovarian collagen and umbilical cord mesenchymal stem cell (UC-MSC) ovarian transplantation plus HRT (premarin combined with provera) (group one), or UC-MSC only ovarian transplantation plus HRT (premarin combined with provera) (group two). Two pregnancies were achieved, one in each group (pregnancy rate 14.2%). In group one, however, the pregnancy was terminated owing to trisomy 21; the patient was 37 years old. The other pregnancy, in group two, was ongoing at the time of publication; the patient was 34 years old (Ding et al., 2018). The small sample size of these studies is their main limitation.

Observational studies

In an observational study by Letur et al. (2004), data from 518 patients who had been treated for POI, including occult POI, and who were waiting for oocyte donation were retrospectively analysed. The occult POI group did not fulfil the European Society of Human Reproduction and Embryology definition of POI, and the causes of the participants' POI were not described. The investigators reported that 17 patients (mean age 31.5) conceived (pregnancy rate 3.3%). They reported 14 healthy babies, one ongoing pregnancy and two miscarriages (Letur et al., 2004). The findings of the observational studies are presented in TABLE 3.

A multicentre retrospective observational study by van Erven (2017) studied 85 women with galactosaemia and POI. Of 21 women who tried to conceive, nine became pregnant (pregnancy rate 42.9%). Among those nine patients, 20 pregnancies were reported, with five ending in miscarriage and one in fetal death at 36 weeks' gestation; median age was 24 years. No details, however, were provided on FSH levels or treatment provided (HRT, oral contraceptive pill or no treatment), and two patients reportedly had regular menses. The retrospective design of these studies is their main limitation.

DISCUSSION

Pregnancies and live births are uncommon in patients diagnosed with POI but are not impossible. Indeed, POI is not always an irreversible condition, and this review highlights that resumption of ovarian function can occur in karyotypically normal patients (Kalantaridou and Nelson, 2000). Premature ovarian insufficiency is a disorder of many diagnoses, some of which are tentative and, notwithstanding scientific advances, most cases of POI remain unexplained. Spontaneous resumption of ovarian function occurs in 25% of patients, and primordial and pre-antral follicles are frequently found in ovarian biopsies from women diagnosed as having POI (Rebar and Connolly, 1990; Bachelot et al., 2016). The preferred medical treatment to assist patients with POI to conceive is oocyte donation. This, however, has several drawbacks. The most obvious and most fundamental barrier is that many women (and their partners) struggle

to accept the concept of their child not sharing their DNA. Most donor oocyte programmes offer pre-treatment counselling to their prospective clients. This is an essential step to maximize the later emotional health of the child and of the family unit, and some couples will turn back at this stage. Furthermore, oocyte donation is not permitted in many countries and others do not permit payment to prospective donors, creating a mismatch between numbers of women willing to donate altruistically and those who require donation. Indeed, in some countries, in which egg donation is altruistic, women may have to wait 2–5 years before they can be treated with donor oocytes (*Agence BioMédecine, 2015*). Moreover, questions remain about the psychological welfare of donor-conceived offspring. The rates of disclosure are impossible to know as yet; however, it is likely that most donor-conceived children are not informed of their origin by their parents (*Zweifel, 2015; Bracewell-Milnes et al., 2018*).

Many protocols have been described for restoration of ovarian function. A great number of pregnancies have been reported for patients treated with HRT or oral contraceptives followed by ovarian stimulation (regardless of whether the initial treatment was designed to restore fertility). Nevertheless, the underlying physiopathology of POI remains unclear. Some argue that lowering circulating concentrations of FSH with exogenous oestrogens may allow downregulated gonadotrophin receptors to regenerate and regain responsiveness to pharmacological stimulation (*Laml et al., 1999*). An associated hypothesis is that a decrease of LH through the same negative feedback could improve egg quality by preventing early luteinization (*Van Kasteren et al., 1995*). In the RCT conducted by *Tartagni et al. (2007)*, the use of oestrogen therapy before ovarian stimulation significantly increased ovulation rates; however, the study was underpowered and the number of patients in that study was low to allow any conclusions to be drawn.

Another approach to induction of ovulation in women with POI has been the use of corticosteroids. The hypothesis is that 'idiopathic' cases of POI may result from an autoimmune disorder, based on the observation that many patients with POI have co-existing autoimmune disorders, including Addison's disease, thyroiditis or myasthenia; in some cases, auto-antibodies are found. Moreover, excess numbers of lymphocytes and plasma cells have been found in ovarian biopsies from some patients with POI. The mechanism of action of corticosteroids is thought to be a reduction in peri-follicular inflammatory macrophages around follicles, which can then restore folliculogenesis from dormant small follicles (*Badawy et al., 2007*). In the RCT conducted by *Badawy et al. (2007)*, ovulation rates were significantly higher in the group treated with dexamethasone. The number of patients in this study was low, and an agonist protocol encompassing a GnRH agonist plus gonadotrophin was also used. It is, therefore, difficult to make conclusions about the actual effect attributable solely to corticosteroids (*Badawy et al., 2007*). Furthermore, a previous RCT did not show any evidence of corticosteroid efficacy in women with POI (*Van Kasteren et al., 1999*).

Another hypothesis is that a pharmacologically mediated decrease in circulating LH and FSH could restore ovarian function has been suggested as the mechanism by which pregnancies occur with HRT or oral contraceptive treatment. An RCT using oestradiol replacement therapy in patients with POI, however, showed no improvement in ovulation rates (*Taylor et al., 1996*). The observed resumptions of ovulation after taking medication to reduce circulating FSH and LH are more likely explained by the presence of remnant small follicles, which may randomly commence folliculogenesis.

More recently, the use of dehydroepiandrosterone (DHEA) has been described in patients with a low ovarian reserve. This improves intra-ovarian environment through IGF-1, increases the production of oestrogen, progesterone and the number of FSH-receptors, resulting in higher number of growing pre-antral and small antral follicles (*Barad and Gleicher, 2006; Walter et al., 2010*; *Yeung et al., 2013*; *Narkwichean et al., 2013*). An RCT was conducted in poor-responder patients in whom DHEA treatment seemed to result in ovulation and pregnancy (*Wiser et al., 2010*). The number of patients, however, was small, not all of the population studied met the criteria for POI and all the pregnancies occurred in patients with secondary infertility, which is a significant confounding factor.

Finally, two new promising approaches are emerging: IVM and stem-cell technologies. The former is based on the premise that some women with POI still have pre-antral follicles. The physiopathology includes mechanical and biochemical signalling pathways. Fragmentation of ovarian tissue *in vitro* seems to disrupt the Hippo signalling pathway, leading to the development of remnant follicles. Then, these fragments are incubated with Akt stimulating drugs (PTEN inhibitor and PI3K activator), promoting follicle growth. Finally, the fragments are replaced and the patient then undergoes FSH superovulation. Three studies have been published using this IVM protocol, with the birth of three healthy babies (*Kawamura et al., 2013; Suzuki et al., 2015; Zhai et al., 2016*).

With stem-cell techniques, here again, the physiopathology is not clearly understood. Some women with POI have achieved a natural pregnancy after bone marrow transplant after chemotherapy (*Hershlag et al., 2002*). The hypothesis is that the attraction of undifferentiated cells in the ovary allows for the regeneration of the intra-ovarian environment and, consequently, the rescue of remnant follicles. This seems to have been confirmed in a study by *Herraiz et al. (2018)* in which an infusion of bone marrow derived stem cells in a xenograft of human ovarian cortex from poor responders transplanted into mice, resulting in promotion of follicular growth to the pre-ovulatory stage and increased vascularization. In another study in which bone marrow derived stem cells was directly injected into the ovaries of poor-responder patients, some of the patients showed improvement in AFC and AMH levels, but the lack of response in some of the cohort highlights that some profiles are probably more prone to respond to this treatment. Five pregnancies were obtained during the follow-up, and three healthy babies were born (*Herraiz et al., 2018*). Both studies, however, included poor-responder patients, not patients with POI. The sole study using stem-cell technology in patients with POI used umbilical cord mesenchymal stem cells associated with HRT treatment, and one pregnancy was ongoing at the time of publication.

These new techniques bring hope for women with POI; yet, the number of studies remains low, and safety and efficacy require more high-quality studies to be completed. Most of the studies included in this review report pregnancy rates between 2.2% and 14.2% for women diagnosed with POI. *van Erven et al. (2017)* reported a pregnancy rate of 42.9% among a group of patients with POI resulting from galactosaemia. This finding cannot be extrapolated to the general population. Moreover, this percentage represents the number of pregnancies in patients who were currently trying to conceive. This creates a selection bias because those women who were recorded as 'not trying to conceive' may have tried previously without success and had given up. The study by *Check et al. (2016)* reporting a pregnancy rate of 60% for women with POI was unpublished and did not undergo peer-review; we therefore decided not to take this high success rate into account. Similarly, as the report by *Mamas and Mamas (2009)* describing a pregnancy rate of 100% included only five patients, we decided not to include this finding because of the small sample size.

The age of the patients at the time of treatment or natural conception has a significant effect on the chance of pregnancy in women with POI. The age of the patients with POI who conceived was not stated in some of the reports included in this analysis; however, where data concerning age were available, the mean age of those who conceived after a diagnosis of POI was 30 years. Oocyte quality is correlated with female age and it is, therefore, unsurprising that a young patient affected by POI is more likely to conceive if ovulation is restored naturally, or through assisted reproductive technology (*Crawford and Steiner, 2015*). Therefore, although pregnancies in this population are rare, they are not impossible, and the clinician should always take into account that patients need to try with their own gametes, with or without success, before moving forward to egg donation, especially if the patient is under the age of 35 years.

This review has several limitations, including small sample sizes, marked heterogeneity and variable quality of the included studies preventing the realization of a meta-analysis. Notwithstanding, this review provides an update on the treatments that have been used to try to help women with POI to achieve pregnancy and the last review of the literature on this topic was conducted in 1999 (*Van Kasteren and Schoemaker, 1999*), and the review of RCT data in 2013 (*Robles et al., 2013*). It also highlights that no new RCTs with the pregnancy rate as a primary or secondary outcome have been reported since 2007.

In conclusion, POI is a complex disease with a wide variety of causes. No treatment for infertility has so far shown superiority. Because of the heterogeneity of the population, RCTs are difficult to set up. For these patients, HRT remains a cornerstone of treatment to optimize bone and cardiovascular health; however, it cannot be considered a treatment for fertility. Recent advances in options such as IVM and stem cell therapy are likely to be the future of treatment and may generate new hope for these patients.

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