

Psychological variables in medically assisted reproduction: a systematic review

Sofia Burgio¹, Concetta Polizzi¹, Giovanni Buzzaccarini², Antonio Simone Laganà³, Giuseppe Gullo⁴,
Giovanna Perricone¹, Antonino Perino⁵, Gaspare Cucinella⁵, Marianna Alesi¹

¹Department of Psychology, Educational Science, and Human Movement, University of Palermo, Italy

²Department of Women's and Children's Health, Gynaecologic and Obstetrics Clinic, University of Padua, Italy

³Department of Obstetrics and Gynaecology, "Filippo Del Ponte" Hospital, University of Insubria, Varese, Italy

⁴Department of Obstetrics and Gynaecology, IVF UNIT, Villa Sofia Cervello Hospital, University of Palermo, Italy

⁵Obstetrics and Gynaecology Unit, "Villa Sofia Cervello" Hospital, University of Palermo, Italy

Abstract

Introduction: The paths of medically assisted reproduction represent the most important scientific progress to cope with the inability to achieve spontaneous conception (SC) and to reach desired parenthood. Couples undergoing assisted reproductive technology (ART) and couples not facing ovulation induction and artificial fertilization show sufficient levels of well-being and psychological adjustment. However, in some cases couples undergoing ART show lower perceived quality of life than couples with SC.

Our aim is to investigate the main psychological variables involved in the special risk condition of medically assisted reproduction and how they could direct specific guidelines to enhance mental wellbeing in dealing with infertility.

Material and methods: In this regard, we performed a systematic review following the PRISMA guidelines. From all the studies included, the considered outcome measures were psychological, social, and relational variables and are presented in a systematic approach.

Results: A total of 14 studies were included in this article, according to our strict inclusion criteria.

Conclusions: Conflicting results have been proven by this systematic review. Even though all underlined the importance of taking charge of the psychological variables in infertility, few studies monitored and evaluated the effectiveness of these interventions. Moreover, none of the selected studies monitored the evolutionary implications of parental competence on the development of children born from ART.

Key words: medically assisted reproduction, psychological wellbeing, ART, developmental psychology, quality of life.

Introduction

Infertility is a condition affecting about 15% of all couples and assisted reproductive technology (ART) represents the most important scientific progress in the quest to cope with this condition and to reach the desired parenthood. Different techniques are used, which include in vitro fertilization (IVF), intra cellular sperm injection (ICSI), cryoconservation of oocytes and embryos, embryo transfers, and every shrewdness to favour the embryo-endometrial lining contract [1–5]. Nevertheless, even if a pregnancy is made possible by ART, it is very hard to go beyond the feelings of grief and loss linked with infertility, especially when considering the difficult hormonal treatment women undergo [6]. Gynaecological conditions such as endometriosis could be responsible for the development of anxiety and depression in such women [7], but the exhaustive ART path-

way can bring more significant psychological distress to both men and women, especially in cases of repeated failures [8]. The medical conditions hindering a spontaneous pregnancy can act as specific psychological risk factors for the development paths of the individual and the couple. These complications include anxiety and depressive disorders, compulsive behaviour to manage anxious states, and inclinations to self-blame [9, 10]. Moreover, the sexual wellbeing of the women is hampered [11].

Most of the studies focus on psychological variables, such as depression and anxiety, disorders that contribute to causing a specific global infertility-stress condition and can influence the maternal/paternal-infant attachment [8, 12].

Concerning the anxiety levels, many aspects have been considered. Some studies focus on how depression and anxiety levels change during pregnancy ac-

Corresponding author:

Giovanni Buzzaccarini, MD, Department of Women's and Children's Health, Gynaecologic and Obstetrics Clinic, University of Padua, Via Nicolò Giustiniani 3, 35128 Padova, Italy,
e-mail: giovanni.buzzaccarini@gmail.com

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ording to the number of ART attempts (first attempt vs. consecutive ART treatments) [9]. Other studies investigate the role of gestational age in decreasing anxiety levels: in particular, these assume that anxiety could be lower after the third month of pregnancy, thanks to the early use of medical checks that can confirm the health of the foetus and the absence of genetic syndromes [13]. Moreover, studies in ART investigate if the psychological maladjustment of couples during fertility treatments, such as anxiety levels, depression, and feelings of helplessness, influence the patients' intentions to comply with treatment [14].

The relationship between anxiety levels experienced during pregnancy and the low quality of maternal and infant prenatal and postnatal attachment has been investigated because anxiety about the survival of the foetus could adversely affect early parenting competence [15].

These studies on anxiety reveal that helplessness and the feeling of lack of control over one's own life could determine a dysfunctional use of coping strategies [16].

In addition to these specific psychological variables, the impact of ART on the quality of life (QOL) and general health of pregnant women in the field of medically assisted reproduction has been investigated [17]. The increased rate of children born after insemination in many cultures has led to the examination of social and demographic characteristics, family backgrounds, reproductive histories, and attitudes towards motherhood in single and cohabiting women seeking treatment with donor semen [18].

Some studies also focus on many kinds of treatment and psychosocial interventions for risk condition management in medically assisted reproduction. These studies refer to the efficacy of the preparatory counselling or mind/body interventions [19].

An additional consideration regarding the quality of family interactions is made for couples undergoing ART; it is necessary to investigate the ability of these parents to accept their parental role, also due to a sense of parental self-efficacy and adequate self-esteem that can have a positive impact on the management of the desired child (Ibid.).

Finally, the risk condition of twin birth inherent in ART and the fact that excessive levels of parental distress can lead to dysfunctional outcomes in terms of family functioning and therefore in terms of child development deserve consideration [20].

All these considerations are fuel for the need for a systematic review that could group all the evidence in psychological wellbeing in ART.

Material and methods

This systematic review followed the PRISMA guidelines for methodology and data extraction. Further-

more, a protocol for this review was registered on PROSPERO in April 2020 (PROSPERO registration number CRD42020169243).

Aim

This systematic review aimed to investigate main psychological variables involved in the special risk conditions of medically assisted reproduction, and how they could direct specific guidelines to enhance mental wellbeing in the condition of infertility.

Study selection process

This systematic review included randomized, controlled, prospective studies of longitudinal design with repeated measures, cross-sectional studies, and baseline data collection in multicentre cohort studies (i.e. study design). The outcome measures considered were psychological variables (i.e. anxiety, depression, infertility related-stress, parental-foetal attachment, coping strategies, acceptance cognition, self-esteem, resilience) and social/relational variables (i.e. social support, QOL, general health, family relation quality, family backgrounds). Moreover, the intervention program evaluated during the medically assisted procreation path, suggesting support treatment (preparatory counselling, mind/body intervention, maladjustment early assessment) to promote parental competence, have also been considered eligible criteria for inclusion in this review.

Studies involving homosexual-parents with donor semen or surrogates' mothers were excluded, as studies which were not published in English language and were published before 2011. In addition, systematic review and meta-analysis were excluded also.

The studies have been identified through database research on PubMed, PsychInfo, MEDLINE, and Google Scholar. In each database, the following key words were searched for: ART and parental competence, medically assisted reproduction and social support, ART and psychological variables. Their synonymous were identified (i.e. medically assisted reproduction in combination with "psychology", "maternal behavior", "maternal-fetal relation").

Data extraction and quality of assessment

Specific information was extracted pertaining to the following: reference (title of papers), source (author and year), study population (age and sample size), aim of the study, intervention program, outcome measures, results and discussion (main issues), and quality assessment (Table 1). The quality of assessment was carried out using a checklist, as described by Kmet *et al.* [19] (Fig. 1), which evaluated, through a 14-item checklist, the following variables: methods description, outcome

Table 1. Characteristics of the articles included in the systematic review

Reference title	Source (author, year)	Study, population sample size	Aim of the study	Intervention program	Outcome measures	Results and discussion main issues	Quality assessment
Impact of a group mind/body intervention on pregnancy rates IVF patients	Domar <i>et al.</i> (2011)	143 women aged 40 years, who were about to begin their first IVF cycle (<i>n</i> = 143).	To determine if a mind/body group intervention was associated with an increase in pregnancy rates in a group of women who were about to undergo their first IVF cycle.	After the Structured Clinical Interview for the Diagnostic and Statistical Manual II, the sample's randomization through computer-generated random numbers. The experimental group was subjected to the mind/body program for infertility. It is a 10-week group stress management program whose focus is on cognitive behaviour therapy, relaxation training, negative health behaviour modification, and social support components all mind/body programs are heterogeneous for patient diagnosis and stage of treatment. Control subjects were told that they would receive a \$50 spa gift certificate for every 3 months that they remained in the study, with a bonus \$100 certificate if they remained in the study for a year. The control patients had the identical amount of contact with the research assistant as the intervention patients.	Clinical pregnancy rate	Infertility patients with varied diagnoses and at different stages of treatment, who participated in the mind/body program for infertility experienced significantly higher pregnancy rates than control subjects. It has been observed in the mind/body program from patient self-reports that physical and psychological symptom improvements are noted beginning approximately midway through the program, and they increase thereafter.	85%
Evaluation of preparatory psychosocial counselling for MAR	Hakim <i>et al.</i> (2012)	135 heterosexual couples consecutively referred to a fertility clinic and 83 chose to participate in some phase of the study (<i>n</i> = 145).	To examine couples' expectations about, and satisfaction with, a single session of preparatory psychosocial counselling provided prior to engaging in MAR. This included an examination of changes in couples' views of counselling after the session.	To measure expectation of counselling' survey, anxiety and depressive symptomatology and infertility related stress through self-report questionnaires administration. Immediately after the counselling session, couples received the 'opinions about counselling' questionnaire.	The expectations of counselling; anxiety and depressive symptomatology; infertility-related stress; opinions about counselling	Most women and men have very positive expectations about preparatory counselling and the perceived benefits exceed these expectations. The women show most elevated symptoms of anxiety and depression with respect to men. Half of the women reported elevated symptoms of anxiety with respect to men. Both women and men with higher levels of global infertility-specific stress expected counselling to be more important than participants reporting lower levels of stress.	82%

Table 1. Cont.

Reference title	Source (author, year)	Study, population sample size	Aim of the study	Intervention program	Outcome measures	Results and discussion main issues	Quality assessment
Psychological impact of single and multiple courses of assisted reproductive treatments in couples: a comparative study	Reis <i>et al.</i> (2013)	The first group (couples undergoing ART treatment for the first time) included 43 couples, and the second group (couples undergoing consecutive ART treatments) included 46 ($n = 89$).	Two main objectives: (1) to analyse the psychological impact (anxiety and depression levels) of ART in infertile couples, either the first or consecutive treatments and (2) to examine gender and group differences.	The levels of anxiety survey before ART treatment were assessed using STAI-Form Y; levels of depression before ART treatment were assessed using the beck depression inventory II.	Anxiety and depression levels	Group 1 (first time of ART) showed greater levels of state-anxiety than couples from Group 2 (undergoing consecutive ART treatment). With respect to global levels of depression, couples from Group 2 showed higher levels than couples from Group 1. In terms of state-trait anxiety in both groups, men reported greater levels of state-anxiety than women. With respect to the full scale of depression, there are significant gender differences, showing higher values in women compared to men.	69%
Maternal-foetal attachment during early pregnancy in Taiwanese women pregnant by IVF	Kuo <i>et al.</i> (2013)	160 women who completed the questionnaires at 9, 12 and 20 weeks gestation.	To describe development of maternal-foetal attachment in early pregnancy in Taiwanese women who conceived by IVF and to explore the influence of physical symptoms, pregnancy-related anxiety, social support, Chinese childbearing attitudes, and foetal awareness on maternal-foetal attachment at 9, 12 and 20 weeks' gestation.	Tool's administration for women who attended the fertility clinic for IVF treatment at the fifth or 6th week of their pregnancy, and at 9, 12 and 20 weeks gestation. The self-reported measures, including: (1) Maternal-Foetal Attachment Scale; (2) Symptoms Checklist; (3) Pregnancy-related Anxiety Scale; (4) Social Support Apgar; (5) Chinese Childbearing Attitude Questionnaire and (6) Awareness of Foetus Scale (for this variables, all participants have been undergoing to ultrasound).	Maternal-fetal attachment and the influence of physical symptoms, pregnancy-related anxiety, social support, Chinese childbearing attitudes, and foeta awareness on maternal-foetal attachment	The maternal-foetal attachment began to develop early during the first trimester of pregnancy, as early as 9 weeks gestation and continued to increase from 9–20 weeks. Chinese childbearing attitude, awareness of the foetus, and social support were found to be the factors in relation to maternal-foetal attachment. Pregnancy-related anxiety during the first half of pregnancy was not found to be a significant predictor of MFA.	81%

Reference title	Source (author, year)	Study, population sample size	Aim of the study	Intervention program	Outcome measures	Results and discussion main issues	Quality assessment
Are patients at risk for psychological maladjustment during fertility treatment less willing to comply with treatment? Results from the Portuguese validation of the SCREENIVF	Lopes <i>et al.</i> (2014)	291 women and 92 men undergoing any stage of fertility treatment (<i>n</i> = 383).	Two main objectives: (1) to investigate the psychometric properties of the Portuguese version of the SCREENIVF and (2) to investigate the relationship between vulnerability to psychological maladjustment and compliance by looking at patients' intentions to comply with treatment.	The SCREENIVF; it's a self-report questionnaire composed of 34 items organized in 5 dimensions that assess risk for maladjustment. Participants were recruited online and at the clinical setting.	Anxiety, depression, helplessness, acceptance cognitions, social support, QOL, compliance intentions	Women and men at risk for psychological maladjustment were equally willing to comply with treatment as those not at risk and no associations between risk factors and compliance intentions were found. However, an unexpected result showed that more anxious patients are less willing to comply with treatment only if they perceive higher control (i.e. lower helplessness).	77%
Are repeated ART treatments and unsuccessful outcome risk factors for unipolar depression in infertile women	Sejbaek <i>et al.</i> (2015)	41050 women who received ART treatment from 1 January 1994 to 30 September 2009, in Denmark.	To investigate if repeated ART treatment cycles were a risk factor of a clinical diagnosis of unipolar depression and to investigate if unsuccessful ART treatment was a risk factor of unipolar depression in a cohort of female ART patients.	The Copenhagen Multi-Centre Psychosocial Infertility Research Program, a register-based, national cohort study.	The outcomes measures were Assisted Reproductive Technology, live birth, and clinically diagnosed depression in a large national study population	Women having received ART treatment who achieved a live birth were at higher risk of a unipolar depression diagnosis compared with women who had not yet given birth to a child. However, repeated ART treatments did not seem to increase the risk of a subsequent unipolar depression diagnosis compared with women with only one treatment cycle. The study showed that women who underwent ART and achieved a live birth had a higher risk of unipolar depression compared with women with no live birth yet. Women giving birth after ART also had an increased risk of any type of psychiatric disorder compared with women with no delivery. The number of ART treatment was not associated with unipolar depression among women undergoing ART treatment.	83%

Table 1. Cont.

Reference title	Source (author, year)	Study, population sample size	Aim of the study	Intervention program	Outcome measures	Results and discussion main issues	Quality assessment
Anxiety, depression, and attachment before and after the first-trimester screening for Down syndrome: comparing couples who undergo ART with those who conceive spontaneously	Udry-Jørgensen <i>et al.</i> (2015)	47 couples had undergone an ART treatment, and 49 had conceived spontaneously were recruited.	Two main objectives: (1) to understand the changes in the psychological status of the parents to be from before to after the first-trimester prenatal screening test at around 12 weeks of gestational age, by comparing state anxiety, prenatal attachment, and prepartum depression in couples from an SC group with couples who had undergone IVF or intracytoplasmic sperm injection, that is, assisted reproductive technology and (2) to identify a subgroup that was particularly vulnerable because of anxiety.	STAI to assess the anxiety, EPDS to measure prepartum depression, and the Maternal and Paternal Antenatal Attachment Questionnaire to measure Prenatal Attachment, before the first-trimester combined prenatal screening test at around 12 weeks of gestational age (T1) and just after receiving the results at approximately 14 weeks of gestational age (T2).	Anxiety, prepartum depression, prenatal attachment	Anxiety decreased significantly in both women and men, as did depression in men. Attachment increased significantly in both women and men. Women in the ART group experienced a greater decrease from T1 to T2 in anxiety than women in the SC group, whose anxiety decreased only slightly. For depression, a similar pattern was observed: Prepartum depression tended to decrease in women from the ART group but was stable in women in the SC group. With regard to the clinical anxiety group, time had no significant effect on depression; anxiety tended to decrease. The increase in attachment was significant.	87%
Depression, pregnancy-related anxiety and parental-antenatal attachment in couples using PGD	Winter <i>et al.</i> (2016)	60 women with PGD, 58 women with intra-cytoplasmic sperm injection and 69 women with spontaneous conception.	To evaluate significant differences between PGD, intra-cytoplasmic sperm injection and SC couple, regard to depression, anxiety, low level antenatal attachment, social desirability.	Questionnaires online in each trimester (T1: 12–14 weeks, T2: 20–22 weeks, T3: 30–32 weeks of gestation) and at 3 months post-partum (T4). To measure depression, the Dutch version of the EPDS was administered. Pregnancy-related anxieties were assessed using the short version of the Pregnancy Related Anxiety Questionnaire. Maternal/Paternal Antenatal Attachment Scale (further: M/PAAS).	Stress assessed by depression and specific anxiety and prenatal attachment	PGD couples are not more at risk of developing depression or pregnancy-related anxieties during and after pregnancy compared with intra-cytoplasmic sperm injection or SC couples. Both maternal and paternal antenatal attachment in PGD couples were comparable to bonding processes in intra-cytoplasmic sperm injection and SC couples. Couples in all three conception groups experienced pregnancy-related anxieties to a comparable extent at every stage of gestation.	77%

Reference title	Source (author, year)	Study, population sample size	Aim of the study	Intervention program	Outcome measures	Results and discussion main issues	Quality assessment
Coping with infertility: comparison of coping mechanisms and psychological immune competence in fertile and infertile couples	Nagy <i>et al.</i> (2016)	84 parents with a child conceived with ART and 84 parents with a naturally conceived child.	To explore characteristics and differences with regard to coping strategies and psychological immune competence of parents with a child conceived with ART, and parents with a naturally conceived child. To evaluate the differences between genders in coping styles among IVF and naturally conceiving couples.	Coping strategies' assessment using the Hungarian shortened version of the Ways of Coping Inventory. Psychological immunity was measured by the Psychological Immune Competence Inventory (so personal resilience resources or psychological antibodies provide immunity against damage and stress).	Coping strategies and the Psychological Immune System acts as a protective apparatus which strengthens invulnerability and raises the coping capacity of individuals	IVF couples can control their emotions in a better way than couples in stressful situations. IVF women reported increased 'Seeking emotional balance' coping than comparison women, suggesting that more use of positive refocusing and distraction during the infertility treatment might have helped them to cope with their problems. Furthermore, getting into a stressful situation, mothers are more prone to seek emotional and social support and avoid confrontation than fathers, apart from the method of conception. IVF couples possess a 'stronger' psychological immune system than parents of naturally conceived children especially as of 'Sense of coherence' and 'Creative self-concept'.	60%
Observed mother-father-child interaction differences in families with MAR conceived twins and singletons	Anderson <i>et al.</i> (2017)	57 families with eighty 6- to 12-year-old MAR children.	To examine reciprocal parent-child interaction behaviours for MAR twins compared with MAR singletons in middle childhood (6–12 years old).	Observational assessment based on focus group and individual interviews with parents of children conceived using MAR. The assessment took place in a room designed to look like a family dining room, with families seated around a dining room table, and they were being recorded. Families were given 15 minutes to discuss 32 statements describing activities or behaviours that may be important to their family. Families were asked to agree on 3–5 statements of most importance and 3–5 statements of least importance to their family. Observational assessments rated the family's interaction quality. Trained observers used five scales (communication, warmth, listener responsiveness, control, and hostility) from the Iowa Family Interaction Rating Scales (IFRS; Melby <i>et al.</i> , 1998).	Family's interaction quality: communication, warmth, listener responsiveness, control, and hostility	Mothers displayed few interaction behaviour differences between twins and singletons. One exception is that mothers were less likely to exhibit hostile or irritable behaviours toward twin relative to singleton children. Fathers showed differences in interactions toward twin relative to singleton children. For example, fathers were less likely to engage in supportive communication with twins, or listen well to twin children, relative to fathers of singletons. Fathers also exhibited greater controlling behaviours, as well as more hostile or irritable behaviour toward twin relative to singleton children.	76%

Table 1. Cont.

Reference title	Source (author, year)	Study, population sample size	Aim of the study	Intervention program	Outcome measures	Results and discussion main issues	Quality assessment
Antenatal paternal adjustment and paternal attitudes after infertility treatment	Pinto <i>et al.</i> (2018)	197 primiparous men (71 after ART and 126 NC).	To explore the interaction effect of mode of conception and depression on antenatal paternal adjustment and paternal attitudes.	Depression and anxiety' assessment with EPDS, and STAI. The Portuguese version of the Paternal Adjustment and Paternal Attitudes Questionnaire (PAPA-AN) – antenatal was used to assess antenatal paternal adjustment and paternal attitudes during the second trimester of gestation (20–28 gestational weeks).	Depression and anxiety, and antenatal paternal adjustment and paternal attitudes	NC men showing high depressive symptomatology had lower antenatal marital relationship satisfaction than NC men showing low depressive symptomatology. ART men showing high depressive symptomatology had lower antenatal marital relationship satisfaction than both ART men showing low depressive symptomatology and NC men showing high or low depressive symptomatology. No associations were found with anxiety.	84%
Effect of preparation for maternal role program on self-esteem of women undergoing IVF	Sallimi Akin Abadi <i>et al.</i> (2018)	60 mothers undergoing IVF were assigned to intervention and control groups.	To determine the effect of a maternal role preparation program on self-esteem of pregnant mothers undergoing IVF.	A demographic characteristics form and Maternal Self-report Inventory (short version). The scale was used before delivery focusing on two dimensions of ability to accept maternal role and expected interaction with the neonate during pregnancy. It should be noted that the control group only received the routine care. For the intervention group, the preparation program consisted in a face-to-face manner for four 2-hour sessions over four weeks in groups of a maximum of 7–8 individuals. Each training session was accompanied by practice, assignments, and an overview of the content of the previous sessions with the cooperation of mothers. Four weeks after completing the first questionnaire, both groups completed the questionnaire again.	Maternal self-esteem and ability to accept maternal role	The maternal self-esteem scores in the intervention group significantly increased after the preparation program relative to those in the control group. The ability to accept maternal role in the intervention group was significantly different from that in the control group after holding the maternal preparation program.	75%

Reference title	Source (author, year)	Study, population sample size	Aim of the study	Intervention program	Outcome measures	Results and discussion main issues	Quality assessment
Assisted reproductive technologies are slightly associated with maternal lack of affection toward the newborn: the Japan Environment and Children's Study	Yoshimasu <i>et al.</i> (2020)	Mothers and children during pregnancy and at 1 year after delivery; mothers were classified in infertility group with ART (n = 2792), infertility group with non-ART treatment (ovulation induction and intrauterine insemination) (n = 3835) and unaided pregnancy group (n = 78726).	To evaluate the association between use of ART and mother-to-infant bonding.	The mother-to-infant bonding assessment with the Japanese version of MIBS-J 17 at 1 year after delivery. The Japanese version of Ages and Stages Questionnaires (ASQ-3) was used to evaluate infant mental and physical development.	Maternal infant bonding, infant mental and physical development, maternal distress during pregnancy	ART did not have any substantial association with LMIB, shown as a low total score of MIBS-J, but non-ART did. ART was found to be associated with the 2 subcomponents of LMIB; however, lack of affection toward infants and anger/rejection toward them. Mothers who undergo ART treatment may have a difficulty in acquiring a self-image as a mother. Significant correlations were observed between mother-to-infant bonding and babies' development as well as maternal psychological distress. Among mothers receiving Assisted Reproductive Technology, some factors were more frequently observed among those with poor mother-to-infant bonding, such as being primiparous, having few family members, having had stressful life events, having negative emotion toward pregnancy, insults from partner during pregnancy.	77%
QOL and general health in pregnant women conceived with assisted reproductive technology: a case-control study	Sarafraz Yazdi <i>et al.</i> (2020)	40 pregnant women conceived with ART and 40 pregnant women who conceived spontaneously.	To evaluate QOL and general health in pregnant women conceived with ART.	A Persian version of WHOQOL-BREF for evaluate QOL. Also, a Persian version of General Health Questionnaire-28 (GHQ-28) was used to evaluate general health in the participants for screening of emotional distress and possible psychiatric morbidity. In the present study, participants completed these two questionnaires twice (once in the first and once in the second trimester of pregnancy).	QOL, general health	The QOL in pregnant women conceived with ART was similar to women conceived spontaneously, in the first and second trimesters of pregnancy. It seems that in infertile women following treatment and after successful conception and during pregnancy, QOL is similar to women conceived spontaneously and is not different. Although during pregnancy these women have high distress levels but by progression of pregnancy and increasing certainty about pregnancy, distress level reduces.	60%

ART - assisted reproductive technology, EPDS – the Edinburgh Postnatal Depression Scale, IVF - in vitro fertilization, LMIB - ????, MAR - medically assisted reproduction, MFA - ???, MIBS-J - Mother-to-Infant Bonding Scale, NC - ???, PGD - preimplantation genetic diagnosis, QOL - quality of life, WHOQOL-BREF World Health Organization Quality of Life-BREF Questionnaire, SC – spontaneous conception, STA1 – State-Trait Anxiety Inventory

Criteria	Yes (2)	Partial (1)	No (0)	NS
1. Question / objective sufficiently described?				
2. Study design evident and appropriate?				
3. Method of subject/comparison group selection or source of information/input variables described and appropriate?				
4. Subject (and comparison group, if applicable) characteristics sufficiently described?				
5. If interventional and random allocation was possible, was it described?				
6. If interventional and blinding of investigators was possible, was it reported?				
7. If interventional and blinding of subjects was possible, was it reported?				
8. Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?				
9. Sample size appropriate?				
10. Analytic methods described/justified and appropriate?				
11. Some estimate of variance is reported for the main results?				
12. Controlled for confounding?				
13. Results reported in sufficient detail?				
14. Conclusions supported by the results?				

Fig. 1. The quality of assessment checklist

assessment, and conclusions. Each analysed study was given a score of 2 if the answer to the item's checklist was yes, 1 if the answer was partial, and 0 if the answer was no or not specified.

Two researchers were involved in giving these scores, and any disagreements were resolved by scores given by a third researcher. The cut-off to consider each examined article as methodologically sufficient was set at 70%; hence, the articles assigned a score lower than 70% were considered with low methodological quality.

Results

The first searches in databases showed a total of 141 papers; according to the PRISMA checklist [21] and inclusion criteria, a more accurate search was performed, selecting 14 papers for data extraction (Fig. 2).

The studies analysed in this systematic review showed a large variety in methodological approach. In detail, 2 of the examined studies used a randomized controlled trial design, 3 were cross-sectional, 4 had a longitudinal prospective, 2 were prospective cohort

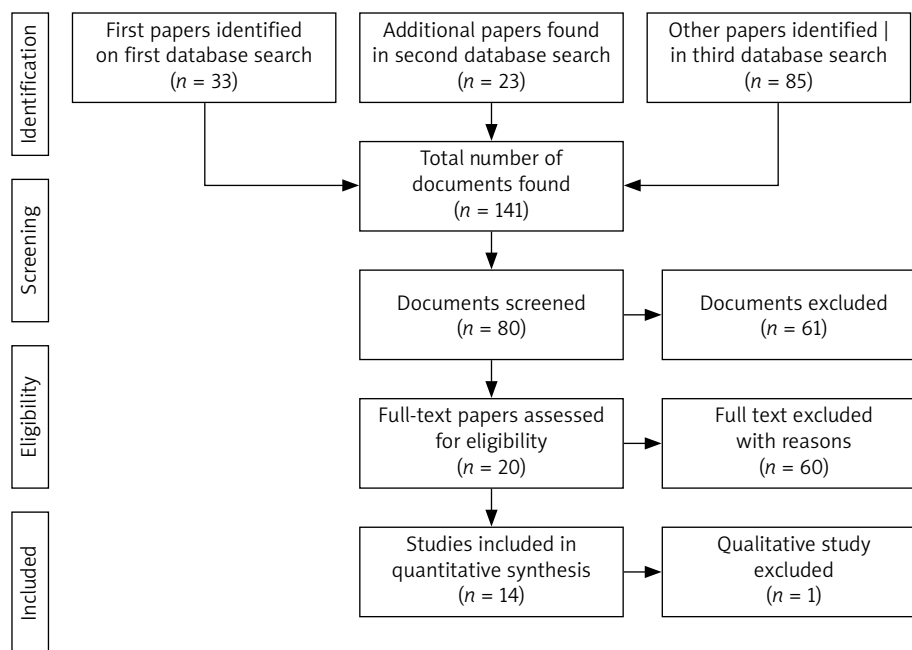


Fig. 2. PRISMA flow chart for the selection of papers to be included in the review

studies, 1 study was explorative, 1 was a case-control study, and another was an observational study.

Twelve papers had a methodological quality higher than 70%, and only 2 studies had a methodological quality lower than 70%.

The samples of participants varied widely, although most studies focused on women [14, 17, 22-26]; more than 2 of these studies considered women in relation to their children and in relation to their partners [14, 25]. Some samples were formed by couples [9, 13, 15, 16, 19], 1 study considered men, and 1 paper included family groups [20, 27].

The variables taken into consideration for the psychological impact assessment of medically assisted procreation reported considerations about anxiety levels, depression, infertility-related stress, prenatal attachment, parental role, coping strategies, QOL, family functioning, and clinical pregnancy rate. Here, the principal results of the studies are reported that obtained higher scores in the quality assessment path [28].

In a study by Udry-Jørgensen *et al.* [11], the analysis of variance (ANOVA) for men and women with ART and spontaneous conception (SC) compared anxiety levels, depression, and attachment scores from 12 weeks of gestational age (T1) and 14 weeks of pregnancy (T2); anxiety scores decreased in both women [$F(1.85) = 11.15, p = 0.001$], and men, [$F(1.81) = 6.38, p = 0.013$]. The same results for depression symptoms were highlighted for men [$F(1.81) = 4.49, p = 0.037$], whereas prenatal attachment was increased in both women [$F(1.85) = 18.27, p < 0.001$] and men [$F(1.81) = 14.92, p < 0.001$].

With regard to male depression symptoms, Pinto *et al.* [25] showed that the prevalence of men with high depressive symptomatology, assessed by the Edinburgh Postnatal Depression Scale (EPDS) (Cox 1987), was higher in the ART group than in the normal conception (NC) group ($z = 3.20, p < 0.001$). According to the results of multivariate analysis of covariance (MANCOVA) and univariate analysis of covariance (ANCOVA), significant multivariate effects of the interaction between type of conception and depressive symptomatology were found on paternal antenatal adjustment and paternal attitudes [Wilks' lambda = 0.43, $F(6.189) = 21.41, p < 0.001, \eta^2 = 0.25$]. Once again, significant univariate effects were found for the marital relationship, attitudes toward sex, and attitudes toward pregnancy and the baby during the second trimester of gestation (all $p < 0.001$).

The ordinal logistic regression analyses using emotional distress, social support, and primary infertility as predictors of expectations for preparatory counselling for women and men in the study by Hakim *et al.* [17] showed significant scores for woman and men in infertility-stress and expectation of counselling as "important" ($0.023, p < 0.05$), although they expected counselling to be "evaluative" ($0.022, p < 0.05$) before participating. In the same way, even men with high

stress levels felt counselling to be "important" ($0.020, p < 0.01$) and "helpful" ($0.020, p < 0.05$).

The significant tests of the linear mixed model conducted by Kuo *et al.* [21] verified the values detected by the Social Support Apgar ($0.45, p < 0.001$), the Chinese Child-bearing Attitude Questionnaire ($0.46, p < 0.001$), and the Awareness of Foetus Scale ($1.29, p = 0.01$) as statistically significant predictors of maternal-foetal attachment.

The analysis of variance conducted by ANOVA test in a study by Salimi Akin Abadi *et al.* [24] showed significant differences in mean scores of maternal self-esteem between intervention and control groups ($p < 0.001$). The intervention group, composed of mothers undergoing IVF, participated in a maternal preparation psychoeducational program, whereas the control group only received the routine care provided by the hospital.

In particular, the intervention group scores were significantly different immediately post-intervention ($M = 42.4, SD = \pm 3.9$) and 1-month post-intervention ($M = 42.5, SD = \pm 4$) ($p < 0.001$). The control group showed no significant differences ($p < 0.31$).

Discussion

The psychological wellbeing of infertile couples is a medical issue that is gaining popularity day by day. In this context both the partners are important, and more effort should be spent in reducing gender-specific differences [29].

The analysis of the results presented in the studies identified 9 main topics falling within psychological and social variables. The first ones included anxiety, depression, stress, and coping strategies; the last ones included maternal-infant attachment, parental role, QOL, and family functioning. Finally, the pregnancy rate was studied as a measure of intervention efficacy.

Anxiety

Anxiety levels, assessed by the state-trait anxiety inventory [30] in most of the studies, decreased as the time of gestation increased. In Taiwanese women, scores were significantly lower at 20 weeks than at 9 weeks [23]. These results are consistent with the literature, according to which pregnancy and the hormones involved make it possible to lower anxiety levels [31, 32]. Moreover, the first screening test of prenatal diagnosis could reduce anxiety in couples undergoing ART and SC [13]. More specifically, women in the ART group experienced a greater decrease after testing compared to women in the SC group, whose anxiety decreased only slightly.

The number of ART attempts was relevant for perceived anxiety; couples who were pursuing ART treatment for the first time showed higher levels of state anxiety compared to couples who had repeatedly undertaken ART [9]. However, some studies have shown that

anxiety tends to increase especially after experiencing several failed attempts and longer treatments [33–35].

Results were discordant regarding the data on men, while in terms of state-trait anxiety, scores were significantly higher among men than among women in both single ART attempt couples and multiple ART attempt couples [9], and there were no associations between the mode of conception (ART vs. SC) and anxiety [27]. However, as the literature suggests, these data underline the importance of male psychological adaptation in clinical practice, which is too often left aside during infertility treatments [36].

In the assessment of anxiety levels as a predictor of couples' expectations for the evaluation of preparatory counselling, half of the women demonstrated elevated symptoms of anxiety, but they were not significant predictors of positive or negative expectations about preparatory counselling [19]. Eleven women out of 72 (15%) displayed psychological disorders, and 6% of men reported clinically significant anxiety levels.

Anxiety was relevant when associated with lower intentions to comply with treatment [14]; indeed, men who presented with high levels of acceptance cognition, in terms of ability to accept one's infertility, showed high anxiety levels, and they were associated with lower intention to comply with treatment.

Regardless of the type of conception paths, couples undergoing preimplantation genetic diagnosis (PGD), ICSI, or SC showed no differences between groups. Couples experienced an increase in anxiety levels in terms of "fear of birth" during gestation and showed a progressive decrease of "fear of an ill child" [15].

Measured 4 times during gestation, "fear of changes" in ICSI and SC couples increased from 12/14 weeks of pregnancy and 30/32 weeks of gestation. More specifically, some gender differences were found: men seemed to be more afraid about birth than women, and they showed anxiety about changes in their life after giving birth.

Depression

The psychological impact of medically assisted procreation is evaluated through anxiety levels associated with depressive symptoms. Despite the lack of significant associations between the number of ART attempts and depressive disorders in a cohort study by Sejbaek *et al.* [22], couples with consecutive ART treatments showed higher depressive symptomatology than couples at first ART attempt [9]; more specifically, women had higher depression levels than men in both first ART attempt and consecutive ART treatment groups.

There are many studies in the literature about depression levels because depression is a widespread condition and is often related to infertility; even after assisted reproductive technique treatments, couples

sometimes fail to overcome the feelings of mourning and loss associated with infertility [37].

However, the results of a Danish cohort study from 1994 to 2009 showed that only 1.3% of women had a certified diagnosis of unipolar depression after experiencing at least one ART attempt [24]; despite these data, it is interesting to note that 64% of the women with live births and 35.7% of the women with no live births received a diagnosis of unipolar depression. This indicates that women with live births had an increased risk of certified depression compared with women with no live births. This is because it is probably more difficult to manage a postpartum depression condition, the construction of parental competence, and taking care of a child, rather than experiencing infertility, mourning, and the loss of not having a child [38].

Prenatal diagnostic tests showed significant decreases in prepartum depression in women undergoing ART; this result was not repeated in women with SC, whose prepartum depression levels were stable before and after the first trimester combined prenatal screening test [13]. These data are not supported by the few studies in the literature showing that during the period of the first-trimester screening test, couples with SC felt the partner was more supportive, which resulted in a lowering of depression and anxiety levels, compared to couples undergoing ART [39].

Regarding levels of men's depression, the ART group showed higher depressive symptomatology than the NC group [40].

In particular, men in the ART group with high depressive symptomatology showed low marital relationship satisfaction in comparison to men in the ART group with low depressive symptomatology and NC with high and low depression levels. Significant differences between groups were found concerning attitudes toward sex; the ART group with high depression symptomatology had less attitude toward sex than both NC with high and low depressive levels. Furthermore, men in the ART group showed significant differences with regard to attitudes towards pregnancy and the baby; the ART group with high depressive symptomatology had more positive attitudes toward gestation and the child than the NC group with high depression levels. Once again, with regard to this attitude, the ART group with low depressive symptomatology reported fewer positive attitudes than the NC groups with high and low depressive symptomatology.

These data are relevant because they can guide clinical intervention in evaluating the psychological well-being of these men; interventions should be targeted based on gender differences [40].

Finally, as for parental competence in terms of paternal adjustment and positive attitudes toward paternity, men in the ART group with high depression levels showed lower paternal adjustment and less positive

paternal attitudes than the ART group with low depressive symptomatology and men in the NC group with high and low depression levels.

However, in a study by Hakim *et al.* [17] only 10% of women and 3% of men showed high depressive symptomatology. Psychosocial counselling intervention is considered less useful by women and men with more depressive symptoms; moreover, counselling sessions were deemed less informative by women with high depression levels. This result leads to further reflection: counselling is often not enough for those who have to manage such a seriously compromised mood [41].

Moreover, the results indicating that women undergoing ART rated the counselling session as less informative are supported by some studies that demonstrate biases in processing and a tendency to attribute negative meaning to neutral stimuli, and enhanced processing of mood-congruent stimuli [42–44].

The hierarchical regression analysis showed a significant effect on the interaction between helplessness cognitions and anxiety and the interaction between helplessness cognitions and depression among women; in particular, patients with high helplessness cognitions and high depression levels were associated with low intentions to comply with the treatment.

Winter *et al.* [13] indicated no significant differences between PGD, ICSI, and SC couples, in which registered depression levels decreased between T1 (12/14 weeks of pregnancy) and T2 (20/22 weeks of pregnancy), with the lowest scores at the third month of the baby's life (T4). However, the SC participants reached the lowest point in terms of depressive symptomatology at T2, and the ART group decreased progressively from T1 to T4.

In the literature, some authors highlight the invasiveness of the PGD pathways, in which even after 3 years, couples perceived high symptoms of depression and anxiety [46]; other authors, however, have not found fluctuations in depressive symptoms during the PGD pathways, compared to what occurs with anxiety levels [47].

Stress

As highlighted by Yoshimasu *et al.* [23], significant correlations were found between maternal distress during pregnancy and at 1 year after delivery: psychological distress conditions during both periods were significantly positively correlated with poor mother-to-infant bonding assessed by the total score of the K6 scale [48] and more precisely with the “lack of affection” and “anger/rejection” subscales. These results are confirmed by the literature showing the presence of high stress levels in medically assisted reproduction paths [49, 50].

Regarding psychological intervention, in both men and women with high infertility-related stress, counselling expectations were perceived as more import-

ant compared to couples with lower levels of stress; in particular, men with high infertility-related stress levels expected counselling to be more helpful, and women evaluated counselling as more important after the session than women with less stress [19].

Maternal-infant attachment

The importance of ART in the maternal and fetal relationship is under debate. For example, interestingly, anger that develops during the ART pathway could be considered as a predictor of weight at birth [50]. In this scenario, the study by Kuo *et al.* [21] shows the scores assessed using the Maternal-Foetal Attachment Scale [51] significantly increased as the pregnancy progressed in Taiwanese women who conceived by in vitro fertilization. In order to analyse significant interactions between covariates (the Symptoms Checklist, the Pregnancy-related Anxiety Scale, the Social Support Apgar, the Chinese Childbearing Attitude Questionnaire, and the Awareness of Foetus Scale) as a factor influencing maternal attachment and weeks of gestation (9–12–20 weeks), the generalised linear mixed model showed no significant interaction, indicating the relation between maternal attachment and each covariate did not change over the weeks of gestation. However, a high score in the Chinese Childbearing Attitude Questionnaire, the Awareness of Foetus Scale, and the Social Support Apgar were significantly associated with high maternal-foetal attachment.

Maternal-infant attachment seems to increase before the first-trimester combined prenatal screening test at around 12 weeks of gestational age (T1) and after receiving the results at 14 weeks of gestational age (T2), as shown by Udry-Jørgensen *et al.* [11]. More specifically, no significant differences were found between ART and SC couples, which indicated an increase in prenatal attachment in both groups, as has been pointed out by some studies in the literature [12]. Regarding the group of 18 women with clinically significant anxiety, they were significantly more depressed and less attached to their foetus than women in the low-anxiety group.

These data are confirmed by Winter *et al.* [13], who showed no difference between groups in couples undergoing PGD, couples in the ART group, and couples with SC. Also in this study, the maternal and paternal antenatal attachment progressively and steadily increased from the first trimester of pregnancy until 3 months post-partum. Many studies confirmed that the attachment increases as the pregnancy progresses, regardless of the conception type [38, 46, 52, 53].

Nevertheless, considering ART mothers undergoing IVF and ICSI, non-ART mothers facing ovulation induction and artificial fertilization, and mothers with unaided pregnancy, non-ART women had a more significantly

positive association with low mother-infant bonding compared to the ART group and the unaided pregnancy group [25]. This provides evidence that the desire for maternity of women in medically assisted reproduction facilitates the construction of the attachment bond, compared to women who have no difficulty in conceiving.

An increased risk of maternal lack of affection, 1 of the 2 components of low mother-infant bonding, seems to be significantly associated with both the ART and non-ART groups.

The assisted reproductive technology and non-ART groups showed significant association with anger/rejection toward babies, the second component low mother-infant bonding. This association is related to multiparous women. With regard to primiparous mothers, undergoing ART was associated with lower risk of anger/rejection toward babies than women with unaided pregnancy.

Moreover, poor mother-to-infant bonding and child development were significantly negatively correlated [54–57].

To analyse the association with low mother-infant bonding and ART mothers, demographic, personal, and medical factors were compared in women with low mother-infant bonding and women without low mother-infant bonding.

The women with lower baby attachment were characterised by a significantly high proportion of primiparity, small families, high stress life-events, no positive feelings toward pregnancy, harassment from the partner, poor health, and infant physical disability.

Parental role and self-esteem

In an Iranian randomised controlled trial study [26], there were significant differences in the mean score of maternal self-esteem between the intervention and control group.

The mean scores of maternal self-esteem among mothers undergoing the preparation program showed, instantly and one month after psychoeducational intervention, significant differences compared to the score shown before the intervention. This difference was not present in the control group.

Maternal self-esteem was assessed before birth through 2 dimensions: attitude to accept the maternal role and expected interaction with the foetus during pregnancy.

As shown by the results of mean scores, the attitude to accept the maternal role was significantly different immediately after finishing the psychoeducational intervention and one month after, compared to what was detected in the phase before the start of preparation program; however, the control group did not show this difference.

Finally, concerning the expected interaction with the foetus, the intervention group revealed significant differences in the mean scores before and just after the preparation program, as well as before and one month after the end of the program. These same significant differences were also found in the control group.

The results of this study showed the functionality and the need for psychosocial interventions with couples in medically assisted reproduction paths [58–61] in a situation where we often tend to focus more attention on the biological and somatic parts of the problem.

Coping

Coping strategies assessed by Nagy *et al.* [14] showed a tendency to use “search for emotional balance” and “withdrawal” in couples with IVF. Moreover, these couples were less oriented to use “emotional and impulsive behaviour”, especially among men.

This indicates that couples who face a medically assisted reproduction path try to have as much control as possible over stressful situations; on the one hand, the literature shows that the feeling that you have good control of events related to fertility and pregnancy is connected to less perceived stress [62, 63]. On the other hand, hyper-control leads to hyper-activation of the arousal responses that could affect perceived stress [64].

With regard to gender differences, women in the IVF group apply each coping strategy more often in comparison with men, whereas this difference was not seen in parents in the group with a naturally conceived child.

A significant difference was found between men and woman in both groups; more specifically, mothers were “seeking social support” more and had a greater tendency towards “withdrawal” than men, regardless of the mode of conception.

Among IVF couples, the ambition for a better emotional balance changed between men and women; these data seem to indicate the presence of emotional difficulties.

Instead, the psychological immune system, understood as the integration of personal resilience resources and adaptive capacities [65], appeared stronger in IVF couples than in the naturally conceived group; the results indicated higher scores in the subscales “sense of coherence” and “creative self-concept” in the ART group.

Quality of life

In Sarafraz Yazdi’s recent study [16], there were no significant differences in the perceived QOL between women in the ART group and mothers with SC in both the first and second trimester of pregnancy. Therefore, in the second trimester the QOL scores increased in both groups compared to what was found in the first period of gestation.

Unfortunately, there is no homogeneity in the results of the studies; the literature highlights inconsistencies between the studies that showed significant associations between poorer QOL and medically assisted reproduction pregnancy [66] and those that indicated higher QOL were associated with ART pregnancy [67].

With regard to the perceived general health, women in the ART and SC groups showed a significant difference at the first and second trimesters. More specifically, women in the ART group showed lower scores in the second trimester compared to those shown in the first period of pregnancy; however, in the control group, general health scores were higher in the second trimester.

Family functioning

In Anderson's observational study [20], parent-child relationships in families with twins or singletons born from medically assisted procreation path, whose age ranges between 6 to 12, was analysed.

Mothers showed few behavioural differences in interaction with twins and singletons: less inclination to be hostile or show irritable behaviours towards twins compared to singletons.

Conversely, fathers showed many differences in the interaction toward twins compared to singletons. They were less inclined to undertake supportive communication and active listening towards twins compared to singletons. Moreover, fathers showed both higher controlling behaviours and hostile and irritable actions towards twins rather than singletons. Male parents tended to have lower communicative positive behaviours, but they also expressed less hostility towards daughters compared to sons.

It might be appropriate to consider the importance of parental competence and the quality of the parents' responsiveness to the child, especially in cases of twin pregnancies, a risk factor that should be avoided in medically assisted reproduction paths [37], because the stress burden may become excessive for the parent.

This study highlighted statistically significant differences between twins and singletons when children's behaviours towards mothers were analysed. In particular, twins were less inclined to show supportive behaviours towards mothers, but at the same time they were less hostile towards their mothers. Thus, twins involved fathers less in supportive communication behaviours compared to singletons, and they showed lower controlling behaviour towards fathers compared to singletons.

Clinical pregnancy rate

Domar *et al.* [28] focused on clinical pregnancy rates among women who were around the beginning of the

first IVF cycle. The selected women were randomised in the mind/body program for infertility (MB) group and control group; the intervention group was subjected to a stress management program through cognitive behavioural therapy, relaxation exercises, and a social support path, whereas the control group was encouraged to participate by an economic reward.

The patients followed for 2 IVF cycles showed no differences in demographic characteristics and clinical conditions in both the MB group and the control group. However, results indicated higher pregnancy rates among patients who took part in the intervention program than the control group; in particular, these differences concern cycle 2 of IVF, while no differences were found during cycle 1.

Some meta-analyses show that psychosocial intervention can have effects on the pregnancy rate, especially because the intervention reduces anxiety, and this increases the possibility of obtaining the desired pregnancy [67]; however, other meta-analyses and systematic reviews underline that the results of the effective influence of the psychosocial intervention on the pregnancy rate are still uncertain due to the low quality of evidence [68].

Final considerations about the infertility pathway

The infertility pathway is a complex path with lots of grief and pain. Often, a multidisciplinary approach is undeniable [69]. Moreover, when approaching oncologic patients [70, 71] who need fertility preservation, a similar medical behaviour should be considered [72]. A noticeable and futuristic medical approach should consider the collaboration of more diversified healthcare professional figures, who join together for the physical and mental wellness of patients. For example, also in complex dangerous situations such as ovarian hyperstimulation syndrome (OHSS) [73], a medical approach should be administered in combination with adequate psychological support.

Conclusions

This systematic review has its key role in presenting the results of the last 9 years of research and studies on the psychological outcomes in an area, such as that of the medically assisted reproduction, which is relatively new and niche. The clinical interventions can be designed starting from the results of these studies; in this way, from a clinical perspective, interventions could allow the collection of data and contribute to the knowledge of the literature, and scientifically guide clinicians to the personalisation of interventions.

The shortcomings include the conflicting results, and although they all underline the importance of tak-

ing charge of the psychological variables in infertility, few studies monitor and evaluate the effectiveness of these interventions from the use of ART to the post-natal period.

Another critical issue is that none of the selected studies monitors the evolutionary implications of parental competence on the development of children born from ART. It would be desirable for future research to focus precisely on these aspects.

Disclosure

The authors report no conflict of interest.

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