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Perinatal Mood and Anxiety Disorders in Women Undergoing Medically Assisted Reproduction

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Abstract: Background: Women taking advantage of medically assisted reproduction (MAR) techniques may differ from spontaneously conceiving women (nonMAR) in risk of depression and/or anxiety. We aimed to investigate possible differences between MAR and nonMAR through the use of the Edinburgh Postnatal Depression Scale in a sample of Italian-speaking women at their third trimester of pregnancy. Methods: We administered the Edinburgh Postnatal Depression Scale (EPDS) to two groups of pregnant women, MAR and nonMAR, at the third trimester of pregnancy (T0), one month after delivery (T1), and three months after delivery (T2) from February 2013 to December 2019. EPDS total scores cutoffs were ≥9 for risk of depression, 9–11 mild depression, ≥12 major depression, and the EPDS-3A cluster ≥4 was a proxy for anxiety. Results: Included were 1303 nonMAR women and 92 MAR, an expected disproportion. NonMAR and MAR women did not differ on depression or anxiety at any assessment timepoint. MAR women were older than nonMAR, consumed more alcohol and medical drugs, and displayed more complications during pregnancy. Scoring over the threshold on depression risk was associated with foreign nationality, unemployment, psychiatric history of the patient, family or partner, psychiatric problems in past pregnancies, hyperemesis, premenstrual syndrome (PMS), and stressful life events in the last year at baseline, and, for some of them, at other timepoints. In contrast, MAR past or current was associated with having suprathreshold depression at the first-month postpartum follow-up. Conclusions: Taken together, our data show that women opting for MAR do not differ from spontaneously conceiving women regarding psychiatric outcomes but do differ on some sociodemographic and clinical variables.

Keywords: perinatal psychiatric disorders; mood disorders; anxiety disorders; medically assisted reproduction; assisted reproductive technology; Edinburgh Postnatal Depression Scale (EPDS)

1. Introduction

Infertility within a couple is the inability to achieve pregnancy after at least one year of targeted unprotected intercourse attempts. It affects about one out of four (20%) heterosexual couples and its global burden in women from 190 countries remained similar in prevalence and trends from 1990 to 2010 [1]. Infertility has been labeled as a "global public health issue" [2]. In recent years, the number of couples who seek infertility treatment is markedly increased [3].

Medically assisted reproduction techniques (MARs or assisted reproductive technologies (ARTs)) include all procedures managing human oocytes, sperm or embryos in the context of a project aimed at achieving pregnancy. A much-needed innovation in medicine, they had a slow development amidst ethical concerns and religious hostility. The British physiologist Robert Geoffrey Edwards (27 September 1925–10 April 2013) began working on rodent oocytes in the late 1950s with his wife Dame Ruth Fowler (December 1930–October 2013), publishing the first seminal paper on superovulation [4]. He eventually associated with gynecologist Patrick Christopher Steptoe (9 June 1913–21 March 1988) from 1968 on, working on in vitro fertilization of human oocytes [5]; the collaboration led to the birth of the first "tube babe" in 1978 [6]. Edwards alone was awarded the Nobel Prize in Physiology or Medicine 2010 (Steptoe was not alive by that time) for "for the development of in vitro fertilization". These techniques may be in vivo (gametes encounter each other in the woman's body, a method called intrauterine insemination (IUI), which has a low per cycle success ratio of about 12%) or in vitro (mainly in vitro fertilization (IVF) with embryo transfer, and intracytoplasmic sperm injection (ICSI)). Fertilization is improperly subdivided into autologous or homologous (both gametes are from the couple) and heterologous (involves gametes from one or more donors). The introduction of ICSI addressed many cases of male sterility, thus reducing the need for donors, and reducing the rate of multiple pregnancies [7].

In Western societies, people marry later than before and seek pregnancy when the couple is at higher risk of infertility due to advancing age, although the existence of psychopathological (depression) or hormonal factors may add to this [8]. This has led to an increase in requests for MAR. This raised the issue of psychological stress related to a diagnosis of infertility or its treatment [9] which may affect the quality of intracouple relationship [10], especially when treatment attempts fail, whereas success usually leads to a reduction in negative emotions [11]. According to a longitudinal US cohort study, failure increases the risk of anxiety and depression, while if anxiety and depression pre-exist to treatment attempts, they do not affect the outcome [12]. In Sweden, when the first IVF fails, two further cycles are offered; however, despite the availability of this free service, several couples decide to withdraw. A longitudinal cohort study investigated the reasons for such withdrawal and found the main determinant to be the psychological distress caused by failure [13].

Women intending to undergo MAR do not differ significantly from the general population on psychological measures [14]. However, an Italian study showed slightly higher anxiety and/or depression rates in both women and partners awaiting IVF/ICSI with respect to the general population, while 18.5% of women and 7.4% of partners who had scored under the threshold at the beginning of the procedures scored above-threshold on anxiety or depression rating scales at the end of the procedures [15]. However, most studies did not find differences in depression between infertile women undergoing treatment for infertility and controls [16–21], and one found its prevalence to be reduced in IVF women compared to controls [22]. Results match the conclusions of systematic reviews and meta-analyses, which ruled out a relationship between MAR and postpartum depression [23,24]. However, one study found more postpartum depression in IVF mothers related to predictors such as caesarean delivery, multiple treatment cycles, and inadequate social support [25,26], while another found, in MAR women, a higher age of the woman, economic difficulties, infertility duration, and multiple unsuccessful attempts to increase depression and a soothing effect of partner support [27]. Women score higher than their partners on anxiety and depression [15,17]; a longer infertility history and having an anxious partner appeared to increase anxiety and depression in IVF women [15]. The main risk factors for the development of perinatal depression in women undergoing MAR were

past major depressive episodes [28] or other psychiatric disorders [18,20], and past unsuccessful infertility treatment cycles, which also increase the odds for anxiety symptoms [16,29].

Psychological stress as a cause of infertility is long debated; the relative risk of infertility of women with a history of depressive symptoms was found to be 2 in one study [30] and another showed twice as many women with infertility to exhibit depressive symptoms compared to fertile women [31]. Infertility secondary to female factors predicts the development of anxiety and stress in the woman, along with strong guilt feelings, which contribute to depression [21]. This phase of increased stress extends from the period prior to initiation of infertility treatment [21] to ovarian stimulation and 10 days after embryo transfer [32–34]. IVF was not found to be related to increased state anxiety compared to spontaneous conception [35–37], but pregnancy-related anxiety focusing on the fetus and newborn was reported to be higher in IVF women than spontaneously conceiving women in some [35,38], but not in other studies by the same investigators [36,37]. Increase in pregnancy-related anxiety, rather than successful child bearing, appears to be related to hormonal stimulation [39]. In another study, IVF women had lower depressive symptoms than spontaneous pregnancy women at the third trimester of pregnancy, but the difference disappeared three months postdelivery; furthermore, the former had higher anxiety scores than the latter at the third trimester and the difference was maintained three months postdelivery [40]. Proposed underlying mechanisms include hyperprolactinemia, alterations in the regulation of the hypothalamic-pituitary-adrenal (HPA) and gonadotropin-luteinizing hormone (GnRH-LH) axes, and hyper- or hypothyroidism [41,42]. Other stress-related factors, such as low socioeconomic status, living in the inner city or degraded neighborhoods, and alcohol habits, may trigger anxiety and depressive symptoms and in turn negatively affect libido, thus resulting in infertility [43].

Summarizing the above evidence, issues relating to the epidemiology of depression and anxiety in women undergoing MAR and to the differences between them and women conceiving spontaneously are not resolved. Thus, we undertook a prospective, longitudinal, observational study to assess anxiety and depressive symptoms in women in their third trimester of pregnancy. To compare MAR with nonMAR women for depression and anxiety at their third trimester and pregnancy and at one-month and three-month follow-ups, we used the Edinburgh Postnatal Depression Scale [44] with its total score as a proxy of depression and its score on the item 3A as a proxy of anxiety.

2. Materials and Methods

2.1. Research Setting

The study was developed in the context of a collaborative screening effort between the Service of Gynecology and Obstetrics of the "San Pietro Fatebenefratelli" Hospital, Rome, Italy, and the "Center for Prevention and Treatment of Women's Mental Health Problems", Psychiatry Service, "Sant'Andrea" University Hospital, Faculty of Medicine and Psychology, Sapienza University, Rome, Italy.

The study was approved by the local ethics committees (Board of the Sant'Andrea Hospital, Rome and San Pietro Fatebenefratelli Hospital, Rome) and the Regional Committee of San Camillo Forlanini, Comitato Etico Lazio 1, with the protocol no.146/12 June 2013, subsequently no.880/17 July 2013, and subsequently modified in 1917 as no.2471/4 December 2017, 1917/CE Lazio 1. We recruited all consecutive women attending fetal monitoring at the Gynecology and Obstetrics unit of San Pietro Fatebenefratelli Hospital of Rome between February 2013 and December 2019.

Participants provided written informed consent prior to participating in the study, in accordance with all applicable regulatory and Good Clinical Practice guidelines and in full respect of the Ethical Principles for Medical Research Involving Human Subjects, as adopted by the 18th World Medical Association General Assembly (WMA GA), Helsinki, Finland, June 1964, and subsequently amended by the 64th WMA GA, Fortaleza, Brazil, October 2013.

2.2. Participants

A total of 1463 women were recruited during their third trimester of pregnancy among those referring to the Gynecology and Obstetrics service of San Pietro Fatebenefratelli Hospital.

Exclusion criteria were failure to provide free informed consent, incomplete comprehension of the Italian language that prevented participants from completing the questionnaires, and age less than 16 years.

Of the 1463 originally included participants, 1395 completed both the Perinatal Interview (PI) and the Edinburgh Postnatal Depression Scale (EPDS) [44,45]; their data were included in the final analysis. Of the original EPDS completers, 1303 were nonMAR and 92 were MAR. Of MAR women, 16 agreed to respond to the 1-month postpartum follow-up and 8 to the 3-month follow-up; of the nonMAR, 279 responded to the 1-month postdelivery and 181 to the 3-month follow-up.

2.3. Measures

Screening tools were administered by physicians and psychologists at the Center for Prevention and Treatment of Women's Mental Health Problems at Sant'Andrea Hospital, Rome, Italy.

Participants completed the following questionnaires:

1. Perinatal Interview (PI): A paper-and-pencil questionnaire to collect sociodemographic and clinical information, allowing us to investigate predictive and protective factors for the development of psychiatric disorders. Besides birth date and place, nationality, educational level, job, and marital status, the PI investigates habits, voluptuary substance use (including tobacco and alcohol), physiological rhythms, past surgery, past and current pharmacological treatment, gynecological and obstetric history, focusing on current and past pregnancies, irregular menses, possible presence of premenstrual syndrome, abortions, unwanted pregnancies, obstetric complications, means by which pregnancy has been achieved (spontaneous vs. MAR), past and current personal and family psychiatric history and possible psychiatric treatments, stressful life events, partner and family/friends' support during pregnancy, and partner data.

2. Edinburgh Postnatal Depression Scale (EPDS) [44]: A 10-item self-rated questionnaire to screen for the risk of depression, anxiety, and suicidal ideation during the peripartum. Initially developed for the identification of postpartum depression [44], the EPDS was later validated for prenatal screening as well [46]. Thanks to its reliability and brevity, this easy-to-complete and interpretive tool became a standard in perinatal care and is recommended by the National Institute for Health and Care Excellence guidelines [47] and cited among the main depression screening instruments by the American College of Obstetricians and Gynecologists [48]. The questionnaire refers to how the woman felt in the last seven days and each item is scored on a Likert-scale from 0 to 3 (variously labeled). Items 1 and 2 assess anhedonia, 3 guilt, 4 anxiety, 5 fear or panic, 6 helplessness, 7 sleep disorders, 8 sadness, 9 tendency to cry, and 10 tendency towards self-harm. Items 1, 2, and 4 are scored 0–3, all others 3–0 (reverse). Higher scores indicate higher risk of depression. In the original English version, a cutoff between 12 and 13 showed 86% sensitivity and 78% specificity; however, the authors suggested a threshold between 9 and 10 for community screening [44]. This cutoff has been endorsed by others [49,50]. Italian validation studies identified 9–10 [45] and 12–13 [51] as optimal cutoffs. Furthermore, the combined score on items 3, 4, and 5 gas is termed EPDS-3A and is assumed as a proxy for the screening of anxiety disorders, with a ≥ 6 cutoff postpartum [52] and ≥4 antenatally [53]. Here we adopted the latter cutoff for risk of anxiety. In the original study, authors recommend to immediately watch the score on item 10 (self-harm) and refer the patient for further evaluation in case score is different from 0. We followed this suggestion strictly. Furthermore, they stratified their sample according to their EPDS score as "depression not likely" (≤8), "depression possible" (9–11), "fairly high possibility of depression" (12–13), and "probable depression" (≥14) [44]. In this study we adopted the

following cutoffs: total EPDS 9–11, "risk of mild depression", total EPDS ≥ 14, "risk of major depression", EPDS-3A ≥ 4: "risk of anxiety disorder", score on item 10 > 0, "suicide ideation".

All women scoring ≥ 12 on the EPDS at T0 (baseline) and an equal number of women scoring <12 at T0 were interviewed and administered the EPDS via telephone at the 1-month postpartum follow-up (T1), and the 3-month postpartum follow-up (T2). All women in a risk category were invited to further clinical and diagnostic assessment and care at the Center for Prevention and Treatment of Women's Mental Health Problems, Sant'Andrea Hospital, Rome. Their results will not be presented here.

2.4. Statistical Analysis

The sample was split into a MAR group and a spontaneous pregnancy group (nonMAR). Groups were compared through one-way analysis of variance (ANOVA1way) on continuous variables, and with the chi-squared test (χ^2) or Fisher's exact test on categorical variables, as appropriate. Cutoff for clinical significance was set at $p < 0.05$.

For all analyses we used the IBM Statistical Package for the Social Sciences software, version 25 (IBM SPSS 25, Armonk, New York, NY, USA, 2017).

To collect literature referring to affective (mood or anxiety) disorders in women undergoing MAR, we used the following search strategy on PubMed: ("Artificial insemination"[ti] OR "Assisted reproduction"[ti] OR "In vitro fertilization"[ti] OR "Intrauterine insemination"[ti]) AND (mania[ti] OR manic[ti] OR mood[ti] OR depressive[ti] OR depression[ti] OR anxiety[ti] OR anxious[ti]), which produced 61 results on 29 September 2020.

3. Results

3.1. Demographic Data of the Total Sample

Mean age in the entire sample was 33.3 years and the range was 16–48. Most women were Italian (N = 1261), 131 were of other nationalities, 1221 were married and/or living with partner, 126 were in a stable relationship, but living alone, 16 were single, 22 were separated/divorced, and 3 were widowed. Most had a higher education, 624 had high school/college education and 673 had graduated, while only 3 had a primary school education and 86 had a middle school education; 1088 had a job and 301 were unemployed.

Voluptuary habits: During pregnancy, 116 were still smokers and 1267 abstained from smoking; 410 had a drink at least once during pregnancy and 969 abstained from alcohol; 9 of the 1386 of the women who responded to this question admitted substance use, while 622 stated to drink caffeine-containing drinks, of whom 13 did so in high quantities, and 745 abstained from caffeine consumption.

Medical and psychiatric history: An active medical condition was present in 273 women (19.9%); of them, 237 were on medical drug treatment. A psychiatric diagnosis was disclosed by 299 (21.7%) participants, mainly anxiety, mood and eating disorders, alcohol and/or substance use disorders, and psychoses, 66 (4.9%) had used psychiatric drugs in the past, and 175 (13.1%) had psychotherapy sessions. Premenstrual dysphoric disorder was admitted by 655 (48.7%) of the sample and rejected by 689 women, while 51 skipped the questions (which investigated mood swings, irritability, sadness, emotional lability, insomnia, and physical symptoms during the week that preceded menses); 355 of 1330 women (26.7%) who responded to questions about family psychiatric history, stated having at least one close relative (parents or siblings) with a psychiatric disorder.

Obstetric history: 382 women had experienced past abortions (29.1%), 96 (6.9%) had been subjected to MAR in the past and 18 of them had received hormonal therapy, 18 IUI, 44 IVF with embryo transfer, 21 ICSI, and 8 had used heterologous fertilization; of the women who used MAR, 11 had used more than one technique. The overall success rate in the MAR population was 51%. Of the women previously subjected to MAR, 49% had conducted one attempt, 23.8% two, 20.9% three, and 5.9% more than three.

Concerning the current pregnancy, 92 women had used MAR; of these, 82 (89.1%) had received hormonal stimulation, 2% (N = 2) had undergone IUI, 3 IVF (3.2%), 3 ICSI, and 2 used heterologous fertilization. Overall, 115 women (8.04%) had used MAR in their lives.

Complications during current pregnancy (threatened abortion/miscarriage, placental abruption, gestational hypertension, pre-eclampsia, gestational diabetes mellitus, placenta previa, and other conditions and events) were present in 375 women and 607 of 1381 reported to have suffered from hyperemesis gravidarum during their current pregnancy. In our sample, 836 (61.8%) women were primiparous; 436 (32.2%) had one child, 4.9% had two, and 1.1% more than two. Among multiparous participants, 63 (12.1%) had suffered from a psychiatric disorder during the previous pregnancy.

Stressful life events: At T0, 36.3% of women (N = 504) reported a stressful life event in the last year, consisting of family conflicts, bereavement, loss of job or financial strain, separation or divorce, and difficulties in relationship with partner.

Perceived support in pregnancy: Partner support during pregnancy was reported by 94.5% of women (N = 1304), support by parents or siblings by 84.5% (N = 1147), and 97.4% (829) believed they would also obtain support in the postpartum period.

Partner data: Mean age of partners was 36.2 years, with a range of 17 to 64 years. Among them, 56% (N = 752) had a high school/college education and 31.9% (N = 429) had graduated; just 2 partners only had a primary school education and 159 had attained a middle school education; 4.6% were unemployed and 95.4% had a job, while 136 (10.1%) had a past or current psychiatric disorder.

Follow-up: Of the 1395 initial participants who had completed the questionnaires at T0, 295 (21.15%) responded to the first postpartum trimester follow-up call (T1), and 189 (13.54%) to the third (T2).

3.2. Scores on the EPDS in the Total Sample

At T0, the EPDS questionnaire was completed by 1395 women; the mean total score was 5.30, with a range of 0–27 points. At risk of depression, using the less sensitive but more specific cutoff of ≥9, were 294 women (21.1%); of them, 123 (8.6%) scored ≥12 (risk of major depression), and 171 (11.9%) in the 9–11 range (risk of mild depression). Thirty-nine women (2.8%) scored ≠0 on the self-harm item 10 of the EPDS, thus they were considered at risk of suicide. Regarding the anxiety item, 3A, the sample scored a mean of 2.5, range 0–9; 452 (47.9%) scored ≥4 and were considered at risk of anxiety (Table 1).

At T1, 295 women (21.1%) responded to the follow-up call; they scored a mean of 5.68 on total EPDS (range 0–27, the same as that of T0), 60 new mothers (20.3%) scored ≥9, thus they were at risk of depression; of them, 43 (14.5%) scored ≥12 (risk of major depression) and 17 (5.7%) in the 9–11 range (risk of mild depression) (Table 1). A total of 10 of 295 women (3.3%) scored ≠0 on item 10 and were considered at risk of suicide; proportions at T1 were greater for both depression and suicide risk than at T0, but this could be due to selection bias, as those scoring high on the EPDS at T0 were specially contacted for follow-up. This did not hold true for the anxiety EPDS 3A cluster, on which 89 women (30.1%) scored ≥4 (Table 1).

At T2, which was the second and final follow-up, 189 women (13.5%) completed the EPDS; mean total score was 3.79 (range 0–24, narrower than T0 and T1). Of these, 26 scored ≥9 (13.7%), hence they were at risk of any depression, 13 (6.8%) scored ≥12 (risk of major depression), and another 13 (6.8%) scored in the 9–11 range (risk of mild depression); 6 (3.1%) women scored ≠0 on item 10 and were considered to experience suicidal ideation (Table 1). Thirty-three women (17.4%) scored ≥4 on the EPDS-3A cluster (Table 1).

Table 1. Edinburgh Postnatal Depression Scale (EPDS), total scores and scores on Item 10 (suicide) and Item 3A (anxiety, range 0–9) at timepoints T0, T1, and T2 in the entire sample (N = 1429).

Timepoint	N	Range	$\bar{x}$ ± SD	EPDS 9–11	EPDS. ≥ 12	EPDS. ≥ 9	EPDS < 9	Item 10 > 0	EPDS-3 $\bar{x}$ ± SD	EPDS-3A. ≥ 4	EPDS-3A < 4
T0	1395	0–27	5.30 ± 4.25	171 (12.2%)	123 (8.8%)	294 (21.1%)	1101 (78.9%)	38 (2.7%)	2.58 ± 2	452 (32.4%)	943 (67.6%)
T1	295	0–27	5.68 ± 5.23	17 (5.7%)	43 (14.5%)	60 (20.3%)	235 (79.7%)	10 (3.3%)	2.41 ± 2.18	89 (30.2%)	206 (69.8%)
T2	189	0–24	3.79 ± 4.46	13 (6.9%)	13 (6.9%)	26 (13.8%)	163 (86.2%)	6 (3.1%)	1.65 ± 1.93	33 (17.5%)	156 (82.5%)

Abbreviations: EPDS, Edinburgh Postnatal Depression Scale; N, number; SD, standard deviation; T0, third trimester of pregnancy, baseline; T1, one month postpartum; T2, three months postpartum; $\bar{x}$, mean.

3.3. Depressive Symptoms and Risk Factors in the Total Sample

We assessed the correlation between depression during and after pregnancy in the general sample, as assessed with the EPDS using the ≥12 cutoff, as well as some risk factors (Table 2).

Table 2. EPDS ≥ 12, N (%), psychiatric and family history, comorbidity, and stressful life events (χ^2 test).

Parameter		Significance
Foreign Nationality		***p* Value**
T0	25 (20.3%)	<0.001 ***
T1	10 (23.2%)	0.027 *
T2	2 (15.4%)	0.747
Unemployment		
T0	37 (30.1%)	0.042 *
T1	19 (44.2%)	0.029 *
T2	4 (30.7%)	0.698
Psychiatric History		
T0	49 (39.8%)	<0.001 ***
T1	17(39.5%)	0.158
T2	3 (23.1%)	0.211
Psychiatric Disorder in Past Pregnancies		
T0	13 (10.5%)	0.002 **
T1	5 (11.6%)	0.28
T2	1 (7.7%)	0.783
Psychiatric Family History		
T0	51 (43.58%)	<0.001 ***
T1	19 (44.2%)	<0.001 ***
T2	5 (38.5%)	0.008 **
Psychiatric History of the Partner		
T0	22 (17.8%)	0.006 **
T1	8 (18.6%)	0.08
T2	3 (23.1%)	0.056
T0	70 (56.9%)	0.001 **
T1	23 (53%)	0.645
T2	5 (38.5%)	0.610
Primiparity		
T0	75 (62.5%)	0.858
T1	26 (63.4%)	0.592
T2	7 (53.8%)	0.362
Complications During Pregnancy		
T0	34 (27.6%)	0.355
T1	14 (32.5%)	0.084
T2	2 (15.4%)	0.895
MAR Current Pregnancy		
T0	11 (8.94%)	0.256
T1	2 (4.65%)	0.004 **
T2	0 (0)	0.303
MAR Previous Pregnancies		
T0	13 (13.5%)	0.093
T1	3 (7%)	0.008 **
T2	0 (0)	0.473

Table 2. *Cont.*

Parameter		Significance
Premenstrual Syndrome		
T0	73 (61.34%)	0.015 *
T1	22 (51.16%)	<0.001 ***
T2	3 (23.1%)	0.001 **
Active Medical Conditions		
T0	24 (19.6%)	0.821
T1	9 (21%)	0.839
T2	3 (23.1%)	0.841
Stressful Life Events Last Year		
T0	67 (54.4%)	<0.001 ***
T1	24 (55.8%)	<0.001 ***
T2	6 (46.2%)	0.036 *

Abbreviations: EPDS, Edinburgh Postnatal Depression Scale; N, number; T0, third trimester of pregnancy, baseline; T1, one month postpartum; T2, three months postpartum; χ^2, chi-squared test; %, percent. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

The correlation was significant across all timepoints (T0, T1, and T2) between risk of depression and positive family history for psychiatric disorders, premenstrual syndrome (PMS), and stressful life events in the last year. At T0, risk factors were foreign nationality, unemployment, positive psychiatric history, psychiatric disorders in past pregnancies, psychiatric history in the partner, and hyperemesis gravidarum. Results were not statistically significant for primiparous women, for those who had obstetric complications or those with concomitant medical conditions. Women who used MAR had a greater risk of depression in the first month postpartum (T1) (Table 2).

When analyzing the entire sample, there emerged a significant correlation between depressive and anxious symptoms ($p < 0.001$) at all timepoints. In the third trimester of pregnancy, 23.7% of the sample had depression and anxiety comorbidity, whereas only 1.8% had depressive symptoms without anxiety. Similarly, in the first and third postpartum months, the frequency of mothers with depression and anxiety was significantly higher than that of mothers without anxiety—34.1% vs. 6.1% at T1 and 39.4% vs. 0% at T2.

3.4. Anxiety and Depression and Other Variables: Comparison between MAR and nonMAR

The sample has been subdivided into MAR (N = 92; 7%) and nonMAR (N = 1303; 93%). Of the initial MAR sample, 16 (17.4%) responded to the 1-month postpartum follow-up (T1) and 8 (8.7%) to the 3-month follow-up (T2); 279 (21.4%) of nonMAR responded to the T1 follow-up and 181 (13.9%) to the T2 follow-up. Their sociodemographic and clinical characteristics are summarized in Table 3, while their scores on the EPDS are shown in Table 4. As expected, the mean age of MAR (36.24, SD ± 5.87) was significantly greater than that of nonMAR (33.10, SD ± 4.99; $p < 0.001$); the same held true for their respective partners (39.75 ± 6.88 MAR vs. 36.00 ± 5.92 nonMAR, $p < 0.001$). MAR used alcohol during pregnancy significantly more often than nonMAR (42.7% vs. 29.3%, $p = 0.006$), were significantly more often on medical treatment (26% vs. 16.5%, $p = 0.016$), and had significantly more frequent complications during the current pregnancy (41.9% vs. 26.2%, $p = 0.001$). Other variables, such as nationality, employment, presence of a partner, perceived support during pregnancy, PMS, past abortions, past psychiatric history or treatments, vomiting during pregnancy, medical conditions, partner support or smoking during current pregnancy did not differ between MAR and nonMAR.

Table 3. Sociodemographic and clinical characteristics of the medically assisted reproduction (MAR) (N = 92) and nonMAR (N = 1303) samples (*p* values reflect Student's *t* for means and SDs, and χ^2 for N and %).

Variables	MAR	NonMAR	*p* Value
Age ($\bar{x}$ ±SD)	36.24 ± 5.87	33.10 ± 4.99	**<0.001**
Age partner ($\bar{x}$ ±SD)	39.75 ± 6.88	36.00 ± 5.92	**<0.001**
Italian nationality, N (%)	85 (87.6%)	1206 (90.8%)	0.3
Has a job, N (%)	81 (83.5%)	1034 (78%)	0.206
Has a partner, N (%)	87 (96.7%)	1251 (96.3%)	1.000
Height (meters)	1.65 ± 0.05	1.65 ± 0.06	0.952
Weight gain end of pregnancy (Kg)	11.33 ± 5.16	11.49 ± 4.5	0.747
BMI before pregnancy	22.57 ± 3.55	22.38 ± 3.5	0.643
Smokes, N (%)	6 (6.2%)	115 (8.7%)	0.389
Uses alcohol, N (%)	41 (42.7%)	385 (29.3%)	**0.006**
Active medical condition, N (%)	25 (26%)	256 (19.6%)	0.129
Medical treatment, N (%)	25 (26%)	217 (16.5%)	**0.016**
Premenstrual syndrome, N (%)	52 (58.4%)	623 (48.4%)	0.066
Psychiatric history, N (%)	27 (27.8%)	282 (21.5%)	0.146
Past psychiatric drug treatment, N (%)	6 (6.2%)	77 (6%)	0.947
Psychiatric family history, N (%)	30 (33.7%)	334 (26.2%)	0.124
Past abortions, N (%)	28 (33.3%)	363 (28.9%)	0.384
Complications in current pregnancy, N (%)	39 (41.9%)	354 (26.2%)	**0.001**
Hyperemesis gravidarum, N (%)	38 (40%)	584 (44.3%)	0.417
Partner support, N (%)	91 (95.8%)	1245 (94.5%)	0.582

Abbreviations: N, number; SD, standard deviation; $\bar{x}$, mean; χ^2, chi-squared test; %, percent. Significant results are highlighted in bold characters.

Table 4. Anxiety and depression: comparisons between MAR (N = 92) and nonMAR samples (N = 1303) (*p* values reflect Student's *t* for means and SDs, and χ^2 for N and %).

EPDS	MAR	NonMAR	*p* Value
T0 (Third trimester of pregnancy)			
EPDS Total score, $\bar{x}$ ± SD	5.34 ± 4.56	5.29 ± 4.23	0.927
EPDS-3A (proxy for anxiety), $\bar{x}$ ± SD	2.54 ± 2.03	2.5 ± 2	0.844
EPDS ≥ 12 (risk of major depression), N (%)	11 (12%)	112 (8.6%)	0.256
EPDS ≥ 9 (risk of depression), N (%)	20 (21.7%)	274 (21%)	0.895
Item 10 ≥ 0 (suicidal risk), N (%)	2 (2.2%)	36 (2.8%)	1.000
EPDS-3A ≥ 4 (risk of anxiety disorder), N (%)	28 (30.4%)	424 (32.5%)	0.730
T1 (One-month postpartum follow-up)			
EPDS Total score, $\bar{x}$ ± SD	4.44 ± 4.42	5.75 ± 5.27	0.330
EPDS-3A (proxy for anxiety), $\bar{x}$ ± SD	2.00 ± 2.03	2.43 ± 2.19	0.445
EPDS ≥ 12 (risk of major depression), N (%)	2 (12.5%)	41 (14.7%)	0.643
EPDS ≥ 9 (risk of depression), N (%)	2 (12.5%)	58 (20.8%)	0.505
Item 10 ≥ 0 (suicidal risk), N (%)	0 (0%)	10 (3.6%)	0.515
EPDS-3A ≥ 4 (risk of anxiety disorder), N (%)	4 (25%)	85 (30.5%)	0.603
T2 (Three months postpartum follow-up)			
EPDS Total score, $\bar{x}$ ± SD	2.38 ± 2.92	3.85 ± 4.51	0.362
EPDS-3A (proxy for anxiety), $\bar{x}$ ± SD	1.25 ± 1.58	1.65 ± 1.94	0.555
EPDS ≥ 12 (risk of major depression), N (%)	0 (0%)	13 (7.2%)	0.303
EPDS ≥ 9 (risk of depression), N (%)	0 (0%)	26 (14.4%)	0.240
Item 10 ≥ 0 (suicidal risk), N (%)	0 (0%)	6 (3.3%)	0.340
EPDS-3A ≥ 4 (risk of anxiety disorder), N (%)	1 (12.5%)	32 (17.7%)	0.354

Abbreviations: EPDS, Edinburgh Postnatal Depression Scale; MAR, medically assisted reproduction; N, number; nonMAR, spontaneous pregnancy; SD, standard deviation; $\bar{x}$, mean; χ^2, chi-squared test; %, percent.

MAR and nonMAR groups did not differ on any of the chosen EPDS measures (total score ≥9, between 9 and 11, ≥12, EPDS-3A ≥4, EPDS-10 ≠0) at any timepoint (Table 4). This was true for both scores analyzed with ANOVA1way and frequencies for being positive for anxiety or depression.

4. Discussion

In this study we investigated depression risk and anxiety symptoms in a group of women at their third trimester of pregnancy who had conceived either spontaneously (nonMAR) or through medically assisted fertilization (MAR) and investigated intergroup differences, either at baseline, and in those who adhered to the follow-up schedule at their first- and third-month postpartum. We found no intergroup differences on depression or anxiety at any assessment timepoint. Between-group differences emerged on some sociodemographic variables, with age being significantly greater in women and their partners in the MAR group than in the nonMAR group, as well as a higher alcohol consumption, medical drug intake, and more complications in index pregnancy in the MAR group. Scoring over the threshold on depression risk was associated with foreign nationality, unemployment, the psychiatric history of patient, family or partner, psychiatric problems in past pregnancies, hyperemesis, PMS, and stressful life events in the last year at baseline, and for some of them, also at other timepoints, while MAR, past or current, was associated with having suprathreshold depression at the first-month postpartum follow-up. Taken together, our data show that women opting for MAR do not differ from spontaneously conceiving woman in terms of psychiatric outcomes.

Our data on perinatal depression in a general population of pregnant women (EPDStotal ≥ 12 8.8% at T0, 14.5% at T1, and 6.9% at T2) are in line with the literature, reporting a peak during the first postpartum months [54–56]. Additionally, the prevalence of anxiety in our sample (EPDS-3A ≥ 4 32.4% at T0, 30.2% at T1, and 17.5% at T2), in line with the literature, is higher than depression and curves down after pregnancy [25,57–60]. This is of particular importance, inasmuch as the presence of an anxiety disorder during pregnancy has been associated to a five-fold increase in the risk of postpartum depression and anxiety [61]; in particular, generalized anxiety disorder represents an independent predictor of postpartum depression [62].

Among risk factors known to be involved in peripartum depression, we confirmed several, but not all. Mood disorder during past pregnancies, positive family psychiatric history, premenstrual dysphoria, foreign nationality, unemployment, and stressful life events in the last twelve months were all correlated with depressive symptoms during the third trimester of pregnancy (T0), as shown in other studies [54,63–67]. Unlike the finding of a large Danish study [68] that primiparous women had more psychiatric symptoms postpartum than multiparous women, in our study primiparae did not display more depressive symptoms than pluriparae. This discrepancy may be due to sociocultural differences and sample size differences. Besides known risk factors, we identified in our sample higher psychiatric symptoms in partners and hyperemesis gravidarum as factors associated with women scoring higher on the postnatal depression scale. Furthermore, the only MAR vs. nonMAR difference here emerged regarded higher depression levels only at the 1-month postpartum follow-up (T1) in the former group, in the face of no difference at T0 and T1; the small size of our sample could be responsible for this difficult-to-explain result, as hormonal stimulation, which is known to affect mood and affect [69], could not have skipped the T0 assessment timepoint. Other factors affecting emotionality, including partner support and success in fertilizing the woman, may also influence the expression of affect changes [70].

Although it is beyond the scope of this study, it is interesting to report on a subsample of women to whom we administered during screening at Sant'Andrea the Mood Disorder Questionnaire (MDQ), that explores bipolar diathesis (Hirschfeld et al., 2000) [71]; MAR women did not differ from nonMAR on this scale and no MAR woman scored suprathreshold on the MDQ. Additionally, preliminary data of our ongoing study at Sant'Andrea of 51 women with postpartum depression derived from the original sample and followed-up at our outpatient service, 15 of whom underwent MAR, did not show

significant differences in depressive and anxious symptom severity from nonMAR, as assessed with the clinician-rated Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale [72].

Despite psychological stress and hormonal stimulation treatments that may expose patients with infertility or subfertility to stress disorders such as depression and anxiety [2], a higher risk of perinatal depressive symptoms has been indicated by one study [17]; our study confirmed in an Italian population the findings of systematic reviews and meta-analyses, showing a lack of correlation between depression and MAR [23,24]. A greater risk of depression in IVF women was also not confirmed by a large Swedish longitudinal study that used the EPDS at the same timepoints as our study [19], and in an Australian study, which found more postpartum adjustment difficulties in women who had gone through several IVF attempts [35,36].

The lack of relationships between perinatal anxious symptoms and MAR we found here has been also reported in control populations by others with self-rating scales [35–37]. Other studies showed similar self-esteem levels in MAR and nonMAR women, and even an increase in self-esteem and lowering of anxiety with pregnancy progression [37,73].

A possible explanation of the lack of a high risk of depression in MAR could be that women with infertility and depression are unlikely to seek MAR, while those seeking it are motivated [74]. Among those initiating IVF treatment, psychological stress represents the first reason for quitting [75]; the determination to carry out the pregnancy could represent a factor that counteracted stress and its disorders, including depression. Accepting the burden of multiple treatment cycles, which are often needed to obtain success, could indicate underlying resilience and effective adjustment strategies [76]. Hence, it is not surprising that the risk of anxiety and depression in MAR is similar to nonMAR, if not less in the peripartum. Recent evidence shows depression to decrease the probability of success of techniques such as IVF with embryo transfer [77]. The increasing availability of infertility treatments, the increasingly earlier diagnosis, and the greater proportion of couples seeking MAR, along with the increased age at which couples wish to have children, may have contributed to destigmatization of infertility. Taken together, these considerations point to the emotional status of MAR women regressing towards the mean and waiving any differences with the emotional status of spontaneously conceiving women.

4.1. Limitations

The main limitation of our study is the reduced sample size of the MAR group, but this could not be otherwise, as just a small proportion of pregnant women use MAR to obtain fertilization. Furthermore, we used only one self-rating scale to assess both anxiety and depression, as well as suicide risk; however, at screening it is difficult to make participants adhere to complicated protocols and there is shortage of time. Besides this, the EPDS is a validated and widely used scale and has been used for the purposes that were our own goals. A strength of this study is that the baseline population had no selection bias. Its ethicality consists of the fact that identified subjects suspected for either depression or anxiety were taken care of by our service and further supported during their postpartum. Another limitation was the low proportion of patients responding to follow-up; changing the setting might have been responsible for such attrition. Furthermore, MAR subsets did not reach a sufficient size to allow for valid statistics, but despite all advantages of ICSI, IVF still represents the bulk of MAR techniques used. The same applies to the homologous/heterologous dichotomization and to the number of past attempts and treatment cycles. It appears that homologous couples present with more anxious/depressive symptoms and higher stress than heterologous couples [78], but it is unlikely that this could have affected our results. A further strength of our study consists of the simultaneous assessment of partners, which showed that psychopathology in couples is matched. The limitations could be considered to be the great sample size difference between MAR and nonMAR, which is due to the low number of women who choose to rely on MAR and represent only a small proportion of the total infertile population, and the lack of use of specific questionnaires to tackle anxiety, such as

the Postnatal Anxiety Screening Scale PASS [79], but the time shortage did not allow us to use other in-depth assessment tools.

4.2. Conclusions

Using MAR techniques appears not to be correlated with an increased risk of depression and/or anxiety in pregnancy and/or in the postpartum period. However, a selection bias in this respect cannot be excluded, as many women with infertility may be discouraged from proceeding with fertilization attempts, thus their underlying depression is not carried over to the MAR sample. As expected, MAR women were older than spontaneously conceiving women, as infertility history and several attempts and treatments are time-consuming. However, we identified clinical characteristics that differ between MAR and nonMAR women, namely, alcohol use, medical treatment, and complications during current pregnancy, all of which were higher among MAR women. The EPDS proved to be a valid screening instrument for identifying depression and anxiety in pregnant women and should be applied to pregnant populations as a standard practice. Future studies should be addressed to the entire infertility population, so to destigmatize infertility and increase the proportion of couples taking advantage of MAR techniques.

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