

PREVENTION OF PERINATAL MENTAL DISORDERS IN WOMEN OF ADVANCED MATERNAL AGE WITH PREGNANCY RESULTED FROM ASSISTED REPRODUCTION

Anna Rubinshtein ✉

*Department of Obstetrics and Gynecology No. 1¹
Leleka Maternity Hospital
56 Kvitky Tsisyk str., Kyiv, Ukraine, 04075
anshantar@gmail.com*

Oleg Golyanovskiy

Department of Obstetrics and Gynecology No. 1¹

*¹Shupyk National Healthcare University of Ukraine
9 Dorohozhytska str., Kyiv, Ukraine, 04112*

✉ **Corresponding author**

Abstract

Women of advanced maternal age (AMA) with pregnancies resulting from assisted reproductive technology (ART) have a high risk of the onset and progression of anxious and depressive disorders, associated with adverse obstetric and perinatal outcomes.

The aim. To improve the mental well-being of pregnant AMA women after ART using the developed algorithm of preventive psychological support.

Materials and methods. The prospective study comprised 150 patients divided into three equal groups of 50 nulliparous women aged 35–45 years with a singleton pregnancy in the cephalic presentation: the main group consolidated of pregnant women after ART who have got routine psychological support; patients with a pregnancy after ART included to the comparison group and patients with a spontaneous pregnancy from the control group were not consulted routinely.

To estimate the psychological condition of the patients the level of maternal anxiety using the Spielberg State-Trait Anxiety Inventory (STAI); sleep quality using Pittsburgh Sleep Quality Index (PSQI); the presence of depressive manifestations using Edinburgh Postnatal Depression Scale (EPDS) were assessed.

Results. We did not observe a significant difference in trait (TA) and state anxiety (SA) levels between the main and comparison groups at terms of 22–24 weeks of gestation; however, these values were significantly lower in the control group. The numbers of patients with high TA and SA levels in the main and comparison groups were also significantly higher than in the control group ($p < 0.05$). We observed no significant increase in TA and SA levels in the main group at gestational terms of 35–37 weeks, in contrast to the comparison and control group. The number of patients with high TA and SA levels in the main group remained significantly lower than in the comparison group. A gradual decrease in TA and SA levels in all groups was observed in the postpartum period, but the differences between the groups remained consistent.

We did not observe a significant difference in sleep quality score between the study groups at terms of 22–24 weeks of gestation. Patients of all study groups reported sleep disturbance with the pregnancy progression, but average PSQI values at terms of 35–37 weeks of gestation and 6–8 weeks after delivery were significantly lower in the main group compared to the comparison group.

The incidence and severity of postnatal depressive symptoms, along with the number of patients at high risk of developing depression in the postpartum, were significantly lower in the main group than in the comparison group.

Conclusions. AMA patients after ART formed a high-risk group for developing anxious and depressive disorders during the pregnancy and postpartum. High anxiety levels compromised sleep patterns have led to poorer quality of life of women. Preventive psychological support for patients during the pregnancy and postpartum enabled early detection and correction of depressive symptoms; validly reduced anxiety levels, improved sleep quality and consequently improved the quality of life of women and prevented adverse obstetric, perinatal, and psychiatric outcomes.

Keywords: advanced maternal age, assisted reproduction, maternal anxiety, postpartum depression.

DOI: 10.21303/2504-5679.2022.002372

1. Introduction

World medical experts estimate that perinatal mental health remains one of the main goals of regional health care systems [1]. Perinatal anxiety disorders differ from normal maternal anxiety

by their intensity and severity, together with a severe adverse effect on the maternal functionality [2, 3]. Concerns about the baby's well-being, pregnancy, labour, possible complications for the baby and mother, a desire to be a good mother, etc. are the general background for perinatal anxiety [4, 5]. Rates of high anxiety and anxiety disorders during pregnancy reach 23 % and 15 %, respectively [6, 7]. High antenatal anxiety appears to be a strong predictor of postpartum depression and is associated with a higher incidence of adverse perinatal outcomes, including preterm labour, nonreassuring fetal status, new-borns admissions to the intensive care unit, and poor neonatal adaptation [8–10]. International studies have shown that the incidence of perinatal depression in high-risk obstetric and perinatal patients could reach 44.2 % [11].

A particular factor of mental wellbeing during pregnancy is adequate quality and duration of sleep. According to a meta-analysis conducted by I. Sedov et al. 2021, the incidence of insomnia during pregnancy averaged 38.2 %, notably in the second trimester it reached 39.7 % [12]. Sleep deprivation is often an isolated disorder but can be caused by high anxiety as well as spontaneously triggering anxious and depressive perinatal disorders. Therefore, if insomnia progresses during pregnancy, early active detection and therapy are crucial for the prevention of psychiatric decompensation [13].

Considering the importance of early detection and treatment of perinatal anxiety, the international experts have recommended a perinatal anxiety screening in a combination with further psychotherapy (behavioural cognitive therapy, meditative concentration, and relaxation techniques) and psychopharmacotherapy, if required [1, 14].

An increase of parental age, especially in the first pregnancy and childbirth, has become a global trend over the past decade. On the one hand, advanced maternal age (AMA) is associated with a higher social and economic status (high education, career, economic independence), psychological stability and more frequent adherence of women to the basic rules of a «healthy way of life». On the other hand, AMA is associated with a significant fertility reduction and a higher incidence of somatic and reproductive disorders, especially obstetric and perinatal complications. Considering the above, an isolated age increase in women with spontaneous and uncomplicated pregnancies is not a risk factor for high anxiety in these patients [15]. However, the group of high obstetric and perinatal risk patients – pregnant women of advanced reproductive age with pregnancy resulting from assisted reproductive technology (ART) requires particular attention in this context. Anxiety in these women is often associated with an adverse reproductive history (a long history of infertility, failure to conceive, reproductive losses, etc.), rather than just the factors common to all pregnant women [16, 17]. Additionally, we suggest that pregnant AMA women after ART should be assigned to a high anxiety group and that preventive psychological support; anxiety levels, sleep quality, depressive symptoms screenings and, if required, psychotherapy and psychopharmacotherapy, should be mandatorily implemented for these patients.

The aim of the study was to improve the mental wellbeing of pregnant AMA women after ART using the developed algorithm of preventive psychological support.

2. Materials and methods

The study was conducted based on Leleka Maternity Hospital (Kyiv, Ukraine) during 2020–2021 years in accordance with the Declaration of Helsinki and approved by the ethics committee of the Shupyk National Healthcare University of Ukraine (protocol number 7, date of approval: 07.10.2019). All the participants signed their informed consent.

The inclusion criteria for this study were the following: maternal age of 35–45 years; nulliparity; singleton pregnancy in cephalic presentation; absence of the fetal congenital defects, maternal severe somatic pathology and uterine malformations. The exclusion criterion was the abnormal fetal position after 37 weeks of gestation.

A sample of 150 pregnant women recruited for the prospective study was equally divided into three groups based on mode of conception and either receiving preventive psychological support (main group, $n_1 = 50$ – IVF conception + psychological support), or not (comparison group, $n_2 = 50$ – IVF conception and control group, $n_3 = 50$ – spontaneous conception). The study groups were representative by social and economic status, somatic anamnesis, and age.

Anxiety levels were measured using the Spielberger State-Trait Anxiety Inventory (STAI-S and STAI-T) in terms of 22–24 weeks of gestation, 35–37 weeks of gestation, in 48–72 hours, and 6–8 weeks after delivery. High anxiety levels were considered to be higher than 45. Sleep quality screenings were conducted in terms of 22–24 weeks of gestation, 35–37 weeks of gestation, 6–8 weeks of postpartum, using the Pittsburgh Sleep Quality Index (PSQI). Sleep deprivation was diagnosed for PSQI scores 5 and higher. Severe insomnia was estimated to be 10 or higher, and a neurologist and psychotherapist were additionally involved in the care of these patients. The postnatal depression manifestations were assessed using the Edinburgh Postnatal Depression Scale (EPDS), being screened in 48–72 hours and 6–8 weeks of postpartum. A score of less than 10 indicated a low risk of depression; a score of 10–13 indicated a borderline risk of depression; patients with a score of 14 or more were at high risk of depression and required the psychotherapist or psychiatrist care.

Patients of the main group received planned psychological consultations, during which they were taught how to formulate/correct their daily schedule (sleeping, eating, resting modes), use of initial meditation techniques of concentration and relaxation for self-correction of psychological discomfort; also, women were mentioned the alarming signs they should be aware of [18–22]. The counselling sessions were conducted in terms of 22–24 weeks of gestation, 35–37 weeks of gestation, 48–72 hours and 6–8 weeks of postpartum, and at the request of the patients. In cases of high anxiety levels, sleep deprivations, cognitive behavioural therapy techniques were used during in-person visits, patients were consulted by a psychotherapist/psychiatrist, and medications (sedatives, antidepressants) were prescribed.

The significance of the difference was assessed using the Student's t-test criteria for continuous variables, and chi-squared and Fisher's exact tests for categorical variables. The level of statistical significance was set at a value of $p < 0.05$.

3. Results

The STAI-S scores at 22–24 weeks of gestation were consistently lower ($p < 0.05$) in the control group compared to the main and comparison groups. At the same time, we did not observe a significant difference of STAI-S values in the main and comparison groups before the start of psychosocial support. The incidences of patients with high (more than 45 points) STAI-S scores in the main and comparison groups were nearly 40 % and was significantly higher than 10 % in the control group ($p < 0.05$).

There was a decrease of STAI-S score in the main group (from 45.3 ± 0.7 to 43.4 ± 0.5 , $p < 0.05$) due to their significant increases in the comparison and control groups at terms of 35–37 weeks of gestation. The mean STAI-S score remained consistently higher in the comparison group compared to the control group (**Fig. 1**). The proportion of patients with high STAI-S scores in the main group was significantly lower than in the comparison group (28 % versus 66 % respectively, $p < 0.05$), whereas in the control group the rate was 46 % and did not significantly differ from the study group.

There were gradual decreases of STAI-S scores in all groups in the postpartum period, but the persistence of differences between the groups remained. Within 48–72 hours after delivery, the number of patients with high STAI-S score in the main group was significantly lower than in the comparison group (14 % versus 48 % respectively, $p < 0.05$), in the control group the rate was 26 %. After 6 to 8 weeks of postpartum the proportion of patients with high STAI-S score in the study groups had no significant differences, ranging from 16 %, 28 % and 12 % in the main, comparison and control groups, respectively.

STAI-T scores were significantly higher ($p < 0.05$) in the main and comparison groups compared to the control group at 22–24 weeks of gestation. The incidences of high (greater than 45 points) STAI-T score in the main and comparison groups were consistently higher ($p < 0.05$) than in the control group, 24 %, 32 % and 8 %, respectively.

STAI-T scores increased in the comparison and control groups with the progress of pregnancy, while in the main group the average STAI-T score decreased considerably (41.9 ± 0.4 vs. 42.3 ± 0.5 , $p > 0.05$). The rate of patients with high STAI-T scores in the study group at 35–37 weeks was 14 % and it was actually lower than rate of 52 % in the comparison group, the control group showed a 30 % rate (**Fig. 2**).

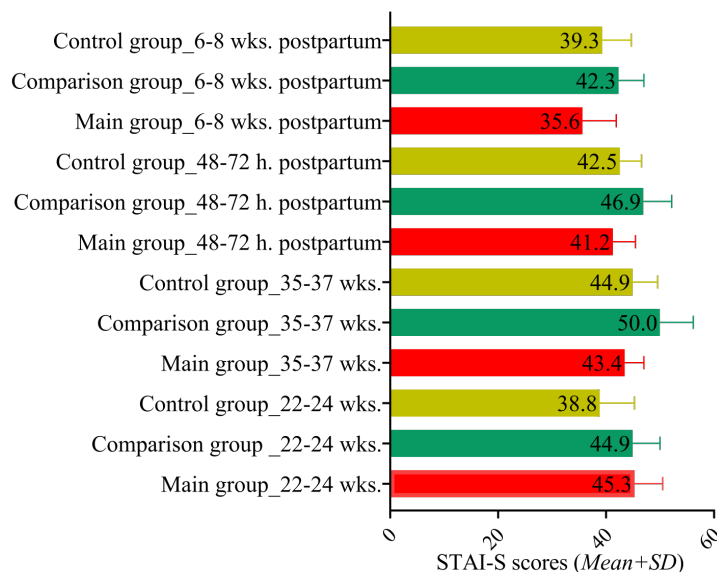


Fig. 1. State anxiety average levels in the study groups

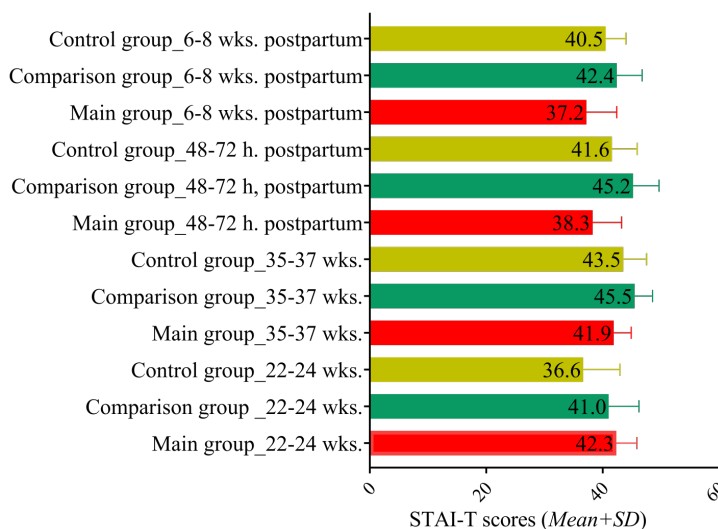


Fig. 2. Trait anxiety average levels in the study groups

STAI-T scores decreased gradually in the postpartum, but there remained a significant difference of the average STAI-T scores in the study groups. The proportion of patients with high STAI-T scores in the study group after 48–72 hours of the postpartum was 10 % but still it was significantly lower than 46 % in the comparison group ($p < 0.05$), in the control group the rate was 22 %. After 6–8 months of the postpartum, the number of patients with high STAI-T scores was 12 % in the main group, 18 % in the comparison group and 10 % in the control group.

At the primary screening stage, sleep deprivations (5 or more points on the PSQI) were found in 80–90 % of patients in all study groups. The mean PSQI score averaged 7, and there were no significant differences between the study groups. The rates of patients with severe insomnia (10 or more PSQI scores) were 4 % in the main group and the comparison group and 8 % in the control group ($p > 0.05$).

Patients of all study groups experienced a deterioration of sleep quality within the pregnancy progressed (**Fig. 3**). The mean PSQI scores were significantly lower in the main group than in the comparison group (7.5 ± 0.3 vs. 8.7 ± 0.3 , $p < 0.05$). The number of patients with significant insomnia also increased and was 12 % in the main group, 26 % in the comparison group, and 18 % in the control group ($p > 0.05$).

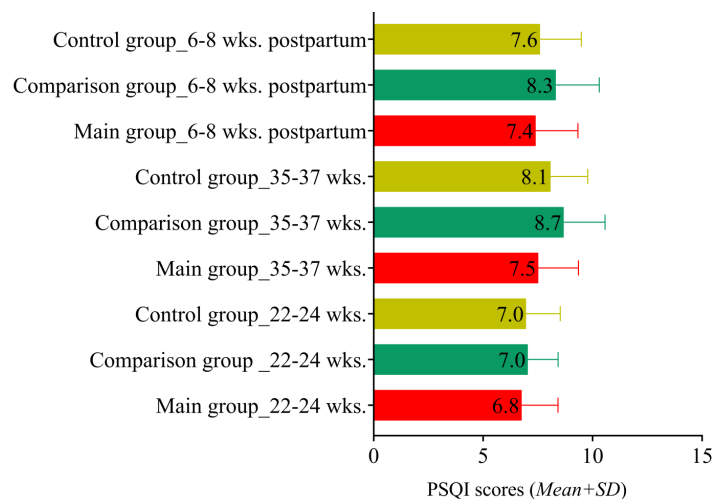


Fig. 3. Sleep quality average levels in the study groups

The average sleep quality indicators remained significantly lower in the main group after 6–8 weeks of the postpartum and were 7.4 ± 0.3 against 8.3 ± 0.3 in the comparison group. There was no significant difference with the control group. The numbers of patients with significant insomnia were relatively stable and remained 18 % in the main group, 28 % in the comparison group, and 16 % in the control group ($p > 0.05$).

The first screening for postnatal depression was performed prior to discharge from the hospital after 48–72 hours of the postpartum. The mean score on the EPDS in the main group was 7.5 ± 0.3 , in the comparison group it reached 9.3 ± 0.4 , in the control group it was 8.2 ± 0.4 ($p_{1,2}; p_{2,3} < 0.05$). The rates of borderline risk of depression (10–13 points on the EPDS) were 16 % in the main group and was substantially lower ($p < 0.05$) than 36 % in the comparison group, in the control group the rate was 20 %. Also, 6 % of women were found to be at high risk of developing postnatal depressive disorders in the comparison group, and these patients were referred to a psychiatrist. The average EPDS scores were 7.0 ± 0.3 in the main group, 9.1 ± 0.3 in the comparison group, and 7.9 ± 0.3 in the control group after 6–8 weeks of the postpartum ($p_{1,2}; p_{2,3}; p_{1,3} < 0.05$). The rates of patients with a borderline risk of depression were significantly lower in the main group than in the comparison group (12 % vs. 38 % respectively, $p < 0.05$), while it didn't change significantly in the control group and equalled 18 %.

4. Discussion

Our study demonstrated that AMA patients after ART had high levels of anxiety, frequent depressive symptoms and severe sleep deprivation during the pregnancy and postpartum periods. Our results match the Williams & Koleva (2018) data that high-risk pregnancies increase the risk for the development of perinatal anxiety disorders and women who had adverse obstetric and perinatal outcomes have also been identified as being at high risk for the development of anxiety disorders [3].

The main factors contributing to the progression of pathological mental symptoms in these patients, besides the standard concerns about the baby, the course of pregnancy and the postpartum period, were an adverse reproductive history, including a long history of infertility and reproductive losses; a combination of these factors formed a consistent negative dominant at the subconscious level. I. Tsakiridis et al. (2019) in their study have confirmed that assisted reproductive technology and a history of infertility have a negative impact on the emotional and psychological wellbeing of pregnant woman and the couple [11]. Previous studies have demonstrated a correlation between high anxiety levels and perinatal depression with adverse obstetrical and neonatal outcomes including preeclampsia, preterm birth, and the higher rates of C-section [8–10].

Most studies to date have focused on the screening and treatment of perinatal anxiety and depressive disorders [19–22], at the same time, the prevention of these disorders in high-risk patients remains unresolved [3, 14]. Considering the high effectiveness of cognitive behavioural therapy

in treating perinatal anxiety and depression, we used some of its meditative techniques as a part of preventive psychological support. In the study it was found that preventive psychological support in AMA patients after ART effectively reduced anxiety levels, improved sleep quality, prevented depression onset and consequently improved the quality of life of women and therefore could have prevented adverse obstetric, perinatal and psychiatric outcomes.

Study limitations. The findings of this study have to be seen in light of some limitations. The first limitation is the lack of prior research studies on the prevention of perinatal anxiety and depressive disorders. The second limitation is that the sample size has been relatively small, which potentially hindering the generalisability of findings. All women included to the study were Ukrainians. This does not guarantee that such our actions will be equally effective in other countries or nationalities. Similar interventions adapted to local health conditions would help to verify the results. The fourth limitation concerns the heterogeneity of the study populations, as women with different types of infertility have been included in the study. Another limitation of our study stemmed from its focus. The focus of our study was the influence of preventive psychological support on anxiety, sleep quality and depression levels but not the obstetrical and perinatal outcomes in a population of AMA women after ART, and not the characteristics of the anxiety and depressive disorders themselves.

Prospects for further research. The results of the study suggest that preventive psychotherapy is effective in AMA women after ART. Further research on the impact of preventive use of cognitive behavioural therapy techniques on obstetric and perinatal outcomes, psychological well-being and quality of life in these women is therefore warranted. Moreover, in future research, a risk stratification system for perinatal mental disorders should be developed, based on the anamnesis and pregnancy and delivery patterns. Further evaluation of the efficacy of preventive psychological support in patients with different high-risk factors for perinatal mental disorders seems particularly important today.

5. Conclusions

Nulliparous AMA women with pregnancy after ART have inherently higher risks of severe perinatal mental disorders and therefore it is appropriate to include complex psychological support in the perinatal care algorithm for these patients. Hence the optimal levels of the patients' psychological comfort would be achieved, maternal anxiety would be reduced, sleep quality would be improved, and postpartum depression will be effectively prevented.

Conflict of interest

The authors declare that they have no conflicts of interest.

Financing

The authors declare there was no financial support.

Acknowledgments

The authors would like to express our gratitude to all those who helped us during the writing of this manuscript. Thanks to LELEKA Maternity Hospital (Kyiv, Ukraine) for providing data for carrying out this study. Thanks to all the peer reviewers and editors for their opinions and suggestions.

References

- [1] Screening for perinatal depression: Committee Opinion No. 630 (2015). *Obstetrics & Gynecology*, 125, 1268–1271. doi: <http://doi.org/10.1097/01.aog.0000465192.34779.dc>
- [2] Thorsness, K. R., Watson, C., LaRusso, E. M. (2018). Perinatal anxiety: approach to diagnosis and management in the obstetric setting. *American Journal of Obstetrics and Gynecology*, 219 (4), 326–345. doi: <http://doi.org/10.1016/j.ajog.2018.05.017>
- [3] Williams, K. E., Koleva, H. (2018). Identification and Treatment of Peripartum Anxiety Disorders. *Obstetrics and Gynecology Clinics of North America*, 45 (3), 469–481. doi: <http://doi.org/10.1016/j.ogc.2018.04.001>
- [4] Guardino, C. M., Dunkel Schetter, C. (2014). Understanding pregnancy anxiety: concepts, correlates and consequences. *Zero to Three*, 12–21.
- [5] Misri, S., Abizadeh, J., Sanders, S., Swift, E. (2015). Perinatal Generalized Anxiety Disorder: Assessment and Treatment. *Journal of Women's Health*, 24 (9), 762–770. doi: <http://doi.org/10.1089/jwh.2014.5150>

- [6] Bayrampour, H., Vinturache, A., Hetherington, E., Lorenzetti, D. L., Tough, S. (2018). Risk factors for antenatal anxiety: A systematic review of the literature. *Journal of Reproductive and Infant Psychology*, 36 (5), 476–503. doi: <http://doi.org/10.1080/02646838.2018.1492097>
- [7] Koukopoulos, A., Mazza, C., De Chiara, L., Sani, G., Simonetti, A., Kotzalidis, G. D. et. al. (2021). Psychometric Properties of the Perinatal Anxiety Screening Scale Administered to Italian Women in the Perinatal Period. *Frontiers in Psychiatry*, 12. doi: <http://doi.org/10.3389/fpsy.2021.684579>
- [8] Ding, X.-X., Wu, Y.-L., Xu, S.-J., Zhu, R.-P., Jia, X.-M., Zhang, S.-F. et. al. (2014). Maternal anxiety during pregnancy and adverse birth outcomes: A systematic review and meta-analysis of prospective cohort studies. *Journal of Affective Disorders*, 159, 103–110. doi: <http://doi.org/10.1016/j.jad.2014.02.027>
- [9] Yedid Sion, M., Harlev, A., Weintraub, A. Y., Sergienko, R., Sheiner, E. (2015). Is antenatal depression associated with adverse obstetric and perinatal outcomes? *The Journal of Maternal-Fetal & Neonatal Medicine*, 29 (6), 863–867. doi: <http://doi.org/10.3109/14767058.2015.1023708>
- [10] Abbas Sadeghian, A., Moghadam, K. B., Baradaran, R., Esmaeilzadeh, M. H. (2019). Evaluation of the Relationship between Prenatal Anxiety and Intra-cesarean Hemorrhage. *International Journal of Medical Investigation*, 8 (3), 40–46.
- [11] Tsakiridis, I., Bousi, V., Dagklis, T., Sardeli, C., Nikolopoulou, V., Papazisis, G. (2019). Epidemiology of antenatal depression among women with high-risk pregnancies due to obstetric complications: a scoping review. *Archives of Gynecology and Obstetrics*, 300 (4), 849–859. doi: <http://doi.org/10.1007/s00404-019-05270-1>
- [12] Sedov, I. D., Anderson, N. J., Dhillon, A. K., Tomfohr-Madsen, L. M. (2020). Insomnia symptoms during pregnancy: A meta-analysis. *Journal of Sleep Research*, 30 (1). doi: <http://doi.org/10.1111/jsr.13207>
- [13] De Chiara, L., Mazza, C., Ricci, E., Koukopoulos, A. E., Kotzalidis, G. D., Bonito, M. et. al. (2021). The Relevance of Insomnia in the Diagnosis of Perinatal Depression: Validation of the Italian Version of the Insomnia Symptom Questionnaire. *International Journal of Environmental Research and Public Health*, 18 (23), 12507. doi: <http://doi.org/10.3390/ijerph182312507>
- [14] Accortt, E. E., Wong, M. S. (2017). It Is Time for Routine Screening for Perinatal Mood and Anxiety Disorders in Obstetrics and Gynecology Settings. *Obstetrical & Gynecological Survey*, 72 (9), 553–568. doi: <http://doi.org/10.1097/ogx.0000000000000477>
- [15] Waldenström, U. (2016). Postponing parenthood to advanced age. *Upsala Journal of Medical Sciences*, 121 (4), 235–243. doi: <http://doi.org/10.1080/03009734.2016.1201553>
- [16] Laopaiboon, M., Lumbiganon, P., Intarut, N., Mori, R., Ganchimeg, T. et. al. (2014). Advanced maternal age and pregnancy outcomes: a multicountry assessment. *BJOG: An International Journal of Obstetrics & Gynaecology*, 121, 49–56. doi: <http://doi.org/10.1111/1471-0528.12659>
- [17] Gong, X., Hao, J., Tao, F., Zhang, J., Wang, H., Xu, R. (2013). Pregnancy loss and anxiety and depression during subsequent pregnancies: data from the C-ABC study. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 166 (1), 30–36. doi: <http://doi.org/10.1016/j.ejogrb.2012.09.024>
- [18] Bedaso, A., Adams, J., Peng, W., Sibbritt, D. (2021). The association between social support and antenatal depressive and anxiety symptoms among Australian women. *BMC Pregnancy and Childbirth*, 21 (1). doi: <http://doi.org/10.1186/s12884-021-04188-4>
- [19] Deligiannidis, K. M., Freeman, M. P. (2014). Complementary and alternative medicine therapies for perinatal depression. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 28 (1), 85–95. doi: <http://doi.org/10.1016/j.bpobgyn.2013.08.007>
- [20] Goodman, J. H., Guarino, A., Chenausky, K., Klein, L., Prager, J., Petersen, R. et. al. (2014). CALM Pregnancy: results of a pilot study of mindfulness-based cognitive therapy for perinatal anxiety. *Archives of Women's Mental Health*, 17 (5), 373–387. doi: <http://doi.org/10.1007/s00737-013-0402-7>
- [21] Milgrom, J., Gemmill, A. W., Ericksen, J., Burrows, G., Buist, A., Reece, J. (2015). Treatment of postnatal depression with cognitive behavioural therapy, sertraline and combination therapy: A randomised controlled trial. *Australian & New Zealand Journal of Psychiatry*, 49 (3), 236–245. doi: <http://doi.org/10.1177/0004867414565474>
- [22] Pugh, N. E., Hadjistavropoulos, H. D., Dirkse, D. (2016). A Randomised Controlled Trial of Therapist-Assisted, Internet-Delivered Cognitive Behavior Therapy for Women with Maternal Depression. *PLOS ONE*, 11 (3), e0149186. doi: <http://doi.org/10.1371/journal.pone.0149186>

Received date 17.02.2022

Accepted date 23.03.2022

Published date 31.03.2022

© The Author(s) 2022

This is an open access article

under the Creative Commons CC BY license

How to cite: Rubinshtein, A., Golyanovskiy, O. (2022). Prevention of perinatal mental disorders in women of advanced maternal age with pregnancy resulted from assisted reproduction. *EUREKA: Health Sciences*, 2, 10–16. doi: <http://doi.org/10.21303/2504-5679.2022.002372>