



Effectiveness of Telephone-based Interpersonal Psychotherapy on Antenatal Depressive Symptoms: A Prospective Randomized Controlled Trial in The Kingdom of Jordan

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Effectiveness of Telephone-based Interpersonal Psychotherapy on Antenatal Depressive Symptoms: A Prospective Randomized Controlled Trial in The Kingdom of Jordan

Abstract

Background: Jordanian pregnant women report high prevalence of antenatal depressive symptoms, compared to their counterparts internationally. One potential non-pharmacological intervention is *Interpersonal Psychotherapy* (IPT), accessed by telephone.

Aim: To compare symptom level in pregnant women with depressive symptoms who received IPT treatment with those who received routine care.

Design: A prospective randomized controlled trial design was used. Following ethical approval, a sample of pregnant women (N=100, 50 in each group), at 24 to 37 weeks gestation, was drawn from one governmental public hospital, which was randomly selected from the list of maternity hospitals in Jordan.

Intervention: Seven sessions (each half an hour) of telephone-based IPT were offered twice weekly to those assigned to the intervention arm: one pre-therapy orientation, up to five intermediates, and one closing session. The Edinburgh Postnatal Depression Scale was administered before and after the intervention. Analysis of covariance was used to detect effects.

Findings: The two groups were matched for demographic and health characteristics. Compared to the controls, pregnant women who received the intervention reported fewer depressive symptoms.

Implications for practice and policymakers: Midwives should screen all pregnant women for symptoms of depression. The provision of brief supportive interventions by midwives, trained in psycho-educational counseling techniques, could be effective in reducing the risk of depression.

Policymakers should make psychotherapists available and accessible in antenatal care units and

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ensure that staff have adequate training via continuing education **programs** to screen for antenatal depressive symptoms.

Key words: antenatal depression; interpersonal psychotherapy; Jordan

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BACKGROUND

Whilst pregnancy can bring much joy, the antenatal period is fraught with challenges including increased incidence of depression (Biaggi et al., 2016). Antenatal depressive symptoms can remain unnoticed and are often under-diagnosed globally (Manikkam & Burns, 2013). In addition, women with antenatal depressive symptoms were more likely to present with postnatal depression (Zejnnullahu et al., 2021).

The incidence of antenatal depressive symptoms differs from one country to another, with higher rates reported in developing countries (Dadi et al., 2020). This is most likely linked with poverty, a social risk factor commonly seen in developing countries (Hartley et al., 2011). In fact, a recent umbrella review revealed that the prevalence of antenatal depressive symptoms is higher among lower-income countries compared to middle-income countries (Dadi et al., 2020). Jordanian pregnant women report higher prevalence rates of antenatal depressive symptoms compared to their counterparts internationally with rates varying between 36.7% (Abujilban et al., 2022) and 57% (Abujilban et al., 2014). This high prevalence rate has led stakeholders and decision-makers to design a strategic plan to prevent and treat antenatal depressive symptoms and mitigate the negative impacts on mother and baby.

In Jordan, antenatal depressive symptoms were more prevalent among women with low-income status, low educational level, higher parity, problems with their mother-in-law, low perceived parenting knowledge, unplanned pregnancy, and low self-efficacy. It was also more prevalent among women who suffer from stress and anxiety and were current smokers (Mohammad et al., 2011). These factors are similar to international studies, in which antenatal depressive symptoms are more prevalent in women with poor social support, difficult financial status, younger age, previous history of depression, prior stressful life events, previous prenatal

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loss, low self-esteem, single marital status, intimate partner violence, and unplanned pregnancy (Manikkam & Burns, 2013; Redshaw & Henderson, 2013).

If left untreated, antenatal depressive symptoms can affect both the mother and infant negatively. During the antenatal period, mothers with depression reported having thoughts of self-harm (Gausia et al., 2009), were more likely to experience preterm birth (Smith et al., 2011), experienced higher risk of inadequate prenatal care, less weight gain, sleep difficulties, substance misuse (Hartley et al., 2011; Manikkam & Burns, 2013), and increased nausea and vomiting, as well as an increased number of visits to the doctor, longer periods of sick leave, and higher rates of planned cesarean birth and epidural analgesia during labor (Andersson et al., 2004). Likewise, babies born to mothers who suffered from depression during pregnancy had increased risk of maltreatment and psychopathology (Goodman, 2012), low birth weight (Kim & Jung, 2012; Smith et al., 2011), sleep problems (Swanson et al., 2010), disorganized attachment (Hayes et al., 2012), increased risk of lower respiratory tract and gastrointestinal infections (Ban et al., 2010), as well as a greater chance of becoming violent by the age of 16 years (Hay et al., 2010).

Worldwide, antenatal depression is treated with pharmacological and non-pharmacological interventions. The most common pharmacological treatment is the administration of selective serotonin reuptake inhibitors (SSRI) such as Fluoxetine, Sertraline and Citalopram (Bandoli et al., 2020; Domingues et al., 2022). On the other hand, non-pharmacological interventions consist of interpersonal psychotherapy (IPT), Computer-Assisted Cognitive Behavioral Therapy (CCBT) (Kim et al., 2014), modified CBT (O'Mahen et al., 2013), acupuncture (Ormsby et al., 2020), and Prenatal Yoga (Lin et al., 2022).

Although it is known that the benefit of pharmacological treatment in pregnancy outweighs the potential risks (Diav-Citrin & Ornoy, 2012), most women prefer not to take

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medication while they are pregnant (Kim et al., 2011). Furthermore, some women may not seek care for their depressive symptoms because of stigma, logistical barriers, decisional conflict, or concerns about teratogenic effects on their babies (Battle et al., 2012). As a result, health care providers are expected to consider effective and efficient non-pharmacological methods of treatment for antenatal depression for all women in general, and Arab women specifically, as they have higher rates of antenatal depressive symptoms (Abujilban et al., 2022) .

Of the non-pharmacological interventions, interpersonal psychotherapy is commonly used for antenatal depression worldwide. International research studies have shown that in randomized clinical trials and open trials IPT was an effective treatment for depression during pregnancy. In fact, some researchers recommend IPT as the first line of treatment for antenatal depression (Grote et al., 2009; Leung & Lam, 2012; Miller et al., 2008; Sockol et al., 2011; Spinelli & Endicott, 2003; Spinelli et al., 2013; Stuart & Koleva, 2014).

In Jordan, antenatal depressive symptoms screening and treatment are not part of the routine antenatal care provided for pregnant women (Department of Statistics(DOS) & ICF., 2019) Thus, women with depressive symptoms are going through their pregnancies without being identified and consequently, not treated. Identifying pregnant women with depressive symptoms and treating them should be a priority in primary health care to prevent the negative consequences associated with antenatal depressive symptoms. Therefore, **for the health and** wellbeing of mothers and their babies, early intervention is crucial (Lenze & Potts, 2017).

Aims

Previous research conducted in Jordan has examined the prevalence, associated factors and predictors of antenatal depressive symptoms (Abuidhail & Abujilban, 2014; Abujilban et al., 2014; Mohammad et al., 2011). **However, to** the authors' knowledge no study has yet examined

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the efficacy of brief IPT for antenatal depressive symptoms in Jordan. Therefore, this study aimed to compare symptoms in Jordanian pregnant women with depressed symptoms who received IPT with those in receipt of usual care in order to address the hypothesis: *Jordanian pregnant women with depressive symptoms who have received IPT will report lower levels of depressive symptoms, compared to pregnant women with depressive symptoms who have not received IPT.*

Ethical consideration

The protocol for the study was approved by the Institutional Review Board of XXX University (#9/2014/2015). The Board confirmed the protection of fundamental human rights. The principle of informed consent was applied. Researchers were available at all times while the women completed the questionnaire in order to answer their questions. The women were assured that their participation in the study was voluntary and that they had the right to withdraw from the study at any time without their decision affecting **their care.**

METHODS

Design

A prospective randomized controlled trial (RCT) was adopted (German Clinical Trials Register: DRKS 00022905) to test the effect of treatment and rule out alternative hypotheses (Polit & Beck, 2011). Pregnant women were screened for depressive symptoms using the Arabic version of the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987). Women with depressive symptoms who scored 12 points and above (Mohammad et al., 2018) were randomly assigned to one of the two study groups: (1) the planned treatment of IPT (intervention group) and (2) the routine Jordanian antenatal care (control group). **Depressive symptom** scores were measured one month later for both the intervention group and the control group. In the case of

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the intervention group, the posttest was administered at the end of IPT treatment, which was one month later. For both groups, the posttest was administered via telephone.

Setting

One Jordanian governmental hospital in the middle region was selected at random from a list of hospitals with more than 6,000 annual births, based on data from the Jordanian Ministry of Health ([MOH], 2011), who were contacted to obtain approval to access the participants as they are the accountable body (Health Law No. 47 of 2008). In Jordan, the MOH provides free health insurance for all pregnant women and is responsible for all levels of care (from primary to tertiary care) delivered in all public and private health sectors (Department-of-Statistics[Jordan] & ICF-Macro, 2010).

Sample

A minimum power of 0.80 was set to enable the detection of between-group differences (Polit & Beck, 2011). Based on an α of 0.05, an effect size of 0.65 (Sockol et al., 2011), and an estimated attrition rate of 20%, a sample of 100 participants (50 per group) was required. The inclusion criteria consisted of: (1) Jordanian pregnant women in their 24th to 37th gestational week; (2) currently experiencing depressive symptoms; (3) between the age of 18 and 42 years old; (4) multiparous and singleton pregnancy; and currently married. Meanwhile, the exclusion criteria consisted of: (1) women with any previously diagnosed mental health problems (including anxiety); (2) who were receiving antidepressant medication; (3) who were receiving psychotherapy or supportive therapy for their depressive symptoms; or (4) currently not living with their husbands. These criteria were employed to decrease the effect of gestational age, parity and risky pregnancies on the findings (Abuidhail & Abujilban, 2014; Mohammad et al., 2011; Sockol et al., 2011).

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Flow of participants through the trial is reported below (figure 1) as recommended by the CONSORT group (Moher et al., 2012). All pregnant women who visited the antenatal clinics (consecutive sampling) during the data collection time were screened for eligibility via interview. Women who met the inclusion criteria and scored 12 and above on the EPDS were randomly assigned to either the intervention group who received the IPT or control group who received the routine care. Three women from the intervention group and one woman from the control group were excluded due to lost communication during the follow up period. Given that the number of participants lost to follow-up were 3.84 % (4 out of 104), and based on the literature recommendation for handling missing data (Dong & Peng, 2013) and multiple imputation decisions (Madley-Dowd et al., 2019), only completed data were included in the final analysis.

---- Insert Figure 1 ----

Intervention

The content of the telephone-based IPT intervention was guided by an adapted manual, developed by a qualified primary clinical psychological therapist, used to facilitate designing interpersonal therapy protocols and session contents based on the worldwide protocols used in general practice among patients experiencing depressive symptoms (Weissman et al., 2000). The manual provided guidance in explaining the IPT phase therapy, problem areas, techniques used in therapy, and strategies utilized in addressing specific IPT problem areas. Intervention plans were validated by three independent experts and subsequently provided by a team of three qualified psychotherapists by telephone (Dennis et al., 2012). To ensure fidelity, the primary therapist trained and supervised the other two psychotherapists on how to apply the program throughout the treatment period. The therapy consisted of three phases: initial (pre-therapy

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orientation), intermediate and closing. Each woman in the intervention group received an individual telephone session twice weekly (up to seven sessions) for a period of one month with each session lasting approximately 30 minutes. For more information on the structure and content of the IPT sessions see Table 1.

---- Insert Table 1 ----

Instruments

Two instruments were used for data collection:

Women's information questionnaire (Abuidhail & Abujilban, 2014; Clark et al., 2009). Socio-demographical and health characteristics were examined using a self-report questionnaire, which was validated by three academic nursing faculty members who agreed on face and content validity and appropriateness for Jordanian culture. These data included: age, marital status, education, income, work status, weight, height, sleeping hours, health status, parity, antenatal care visits problems during current pregnancy, pregnancy plans, previous pregnancies, breastfeeding plans, health care provider, and social support.

Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987): The EPDS is a self-administered 10-question screening tool that was originally validated for use in identifying symptoms of postpartum depression (Levis et al., 2020). The EPDS was utilized in the current study to screen for antenatal depressive symptoms among Jordanian pregnant women. It was used to examine the intensity of depressive symptoms that were present within the previous seven days and takes approximately five minutes to be completed. Each of the 10 items was scored on a 4-point Likert scale, which ranged from 0 (*not at all*) to 3 (*most of the time*) yielding total scores that range between 0 - 30. Different cut-off scores have been used to denote the presence of antenatal depressive symptoms, most of which ranged from 10 to 13 (Levis et al.,

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2020). In this study, 12 points was used as the cut-off score. It is important to note that **item number 10 of the EPDS examines** suicidal thoughts. Thus, any woman who scores between 1 and 3 on item 10 may require an immediate assessment before she leaves the clinic and, after obtaining the woman's and her care provider's approval, appropriate referrals should be made where indicated (Cox et al., 1987). The current study followed this protocol. The EPDS reported sensitivity and specificity of 86% and 78%, respectively (Cox et al., 1987) and has been found to be valid and reliable in Jordanian people with a reported internal consistency during **pregnancy with values** of 0.81 and 0.79 reported for Cronbach's alpha (Abujilban et al., 2014; Mohammad et al., 2011). In the current study, the EPDS scale showed good reliability, with a Cronbach's α of 0.88. The EPDS was administered in both the intervention and control groups on two occasions: pretest and posttest (one month later).

Data collection procedure

The data were collected by two research **assistants** who were trained comprehensively by the PI on how to approach and recruit possible participants and on how to use the study questionnaire for screening and data collection. The research assistants visited the Mother and Child Health Outpatient Clinic at the selected hospital where they invited potential participants who met the inclusion criteria to participate in the study. Women who met the inclusion criteria and were willing to participate were given a consent form and were asked to sign the form. Next, the participants were screened for the presence of antenatal depressive symptoms. The EPDS screening tool was self-administered by the women themselves within a time limit of 30 minutes. All pregnant women who met the inclusion criteria were informed before they consented that they would be randomly assigned to either an intervention group or a control group. Women who scored 12 and above were asked to select a closed envelope (random assignment) (Mohammad et

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al., 2018), which placed them either in the intervention group or the control group. The participants in the intervention group received the planned IPT treatment. Meanwhile, those assigned in the control group received the routine care package, which included measuring pregnant women's weight and blood pressure, as well as performing an ultrasound of the fetus. Pregnant women in the control group whose EPDS scores remained high in the posttest were informed about their depressive symptoms and were provided with contact information to enable them to receive counseling and consultation support. Women who screened negative were thanked for their precious time. For both groups, posttest was administered via telephone one month later.

Data analysis

Descriptive and inferential statistics were computed using IBM SPSS Statistics (Version 23) predictive analytics software. Means and frequency distributions were calculated to describe the sample's characteristics and main variable. The independent t-test was used to detect whether there were any significant mean differences between the intervention group and the control group in regard to the demographic and obstetrical characteristics. Analysis of covariance (ANCOVA) was used to detect the effect of the intervention. Correlation coefficients were performed to examine the relationships between the study's variables. The significance level was set at $p < .05$. All assumptions of regression slopes were met. The study's independent variable was the study group, and the dependent variable was the EPDS's posttest scores. For the dependent variable (posttest value), the covariate was the EPDS's pretest scores (Polit & Beck, 2011). The EDPS's pretest scores were included in the ANCOVA due to its potential effect on the depressive symptoms' score and because it also differed significantly between the two study groups. The model fit of the ANCOVA was assessed using the R-squared (R^2) statistic.

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RESULTS

The total sample was 100 pregnant women, 50 participants were randomly assigned to the intervention group and the remaining 50 to the control group. The women's gestational age ranged from 24 to 37 weeks (*Mean (M) = 31.3, Standard Deviation (SD) = 4*) and the mean age was 29 years (*SD = 5.2*). Most of them (67%) had at least a secondary school level of education with an average of 11.3 (*SD = 3.5*) years at school of which only five women were currently working. The majority of the women were living in a nuclear family household (64%). Almost all of their husbands were working (97%) and the majority of **the husbands** had at least a secondary school level of education (61%). The majority (77%) of the women **did not complain of any health problems during pregnancy**, attended regular antenatal visits (*M = 8.7 visits, SD = 3.7*) where they underwent an ultrasound assessment at each visit. Approximately 80% of them were living near the hospital and all women lived in the city. Around 43% of them had a Hb level of less than 11 gm/dl (a cut-off for low hemoglobin).

Independent samples t-tests were performed to compare the means of the **demographic** and obstetrical continuous variables (age, gestational age, income, number of years of education, number of antenatal visits, gravida, number of children, number of miscarriages, and Hb level) between the intervention and control groups: no significant differences were found between the two study groups. Similarly, Chi-square tests confirmed the proportions of **demographic** categorical variables (employment, husband's employment status, husband's education, health problems during pregnancy) were not significantly different between the two study groups (See Table 2).

----- Insert Table 2 ----

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An independent sample t-test was also used to examine the EPDS pretest scores of the intervention group and control group. The result revealed that there was a small but significant difference in the mean scores of the intervention group ($M = 19.3$, $SD = 3.6$) and the control group [$M = 17.8$, $SD = 2.8$; $t(100) = 2.4$, $p = 0.047^*$]. Therefore, the possible effect of the pretest score was controlled for using statistical analysis (ANCOVA).

Effect of telephone-based interpersonal psychotherapy on depressive symptoms

To identify the potential effect of telephone-based IPT intervention on pregnant women's level of depressive symptoms, a one-way between-groups ANCOVA was performed. After adjusting for the pretest scores on the EPDS, the control group's mean depressive symptoms score on the posttest was found to be significantly higher than that of the intervention group [$F = 50.74$, $p < .001$, partial eta squared = 0.34, control group mean = 16.42 (4.35), intervention group mean = 8.88 (5.82)] (See Table 3). There was no relationship between the pre-intervention and post-intervention scores on the EPDS, as indicated by the partial eta squared value of 0.00, which indicates a very small effect.

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DISCUSSION

This study is one of the first to examine the effect of interpersonal psychotherapy on antenatal depressive symptoms among pregnant Jordanian women. The study targeted pregnant women who were suffering from antenatal depressive symptoms (EPDS score ≥ 12). However, when demographic characteristics of the participants were compared with the Jordan Population and Family Health Survey (JPFHS) (Department of Statistics (DOS) and ICF, 2019), the sample may not be representative of the of pregnant women in Jordan because 51.5% of the participants were ≤ 29 years old, whereas only 30% of married women in the JPFHS were ≤ 29 years old.

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Moreover, 53% of married women and 45% of men in the JPFHS (DOS and ICF, 2019) have completed secondary school or a higher level of education, whereas 67% of the participants and 61% of the participants' husbands had at least a secondary school level of education. In the JPFHS (DOS and ICF, 2019), 14% of women and 55% of men were employed, whereas in the current study only 5% of women and 97% of men were employed. On the other hand, the demographics of our sample were similar to those of the women with antenatal depressive symptoms in the study conducted by Abuidhail and Abujilban (2014). For instance, the mean age of the participants was 29 years, the mean number of years of education was 11.3, and the mean household income was 375.5 Jordanian dinars (JD), all of which were similar to the findings reported by Abuidhail and Abujilban (2014). This implies that the current sample maybe representative of other pregnant women in Jordan who suffer from depressive symptoms.

When comparing the socio-demographic and health characteristics of the two study groups (intervention and control), there were no significant differences between the two groups. This result indicates that the two groups were well matched in terms of their age, income, education, employment, husband's employment status and level of education, gestational age, number of antenatal visits, ultrasound, gravida, number of living children, miscarriages, Hb level, and health problems during pregnancy. This means that the effect of confounding variables was controlled and the study possessed a high degree of internal validity, which enabled the researchers to rule out most of the alternative explanations for the results (Polit & Beck, 2011).

According to the findings of the study, the IPT intervention was found to be effective in decreasing depressive symptoms among Jordanian pregnant women within a **short period of time** (one-month period). This **was manifested** by the intervention group having significantly lower posttest EPDS scores (equating to lower depressive symptoms), despite **having a** pre-existing

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significant difference in depressive symptom scores between the intervention group and the control group (where the control group had lower pretest depressive symptom scores). One possible explanation for the positive effect of IPT is that IPT has a predetermined structure and content that is applied in a specific period of time. The limited timeline of the psychotherapy sessions seems to have motivated and encouraged both the participant and the psychotherapist to focus on a relatively narrow and specific interpersonal problem and to support a change in the participant's behavior and situation to ameliorate that problem. Hence, this approach may have resulted in achieving the psychotherapy goals and relieving the symptoms quickly and effectively (Weissman et al., 2000). Another explanation for this result could be the willingness of Jordanian pregnant women to actively participate in the IPT in order to achieve a desirable outcome in what, for them, is considered a new experience largely because the governmental health sector in Jordan does not typically integrate this type of psychotherapeutic intervention into their routine antenatal care.

The positive impact of IPT on the antenatal depressive symptoms of the Jordanian pregnant women in the current study aligns with previous worldwide studies that have reported a reduction in the level of depressive symptoms among pregnant women after the treatment (Grote et al., 2009; Leung & Lam, 2012; Miller et al., 2008; Sockol et al., 2011; Spinelli & Endicott, 2003; Spinelli et al., 2013; Stuart & Koleva, 2014). Furthermore, the use of telephone sessions was effective in reducing the attrition rate for a follow-up study of this kind because we lost communication with only four participants (See Figure 1). The study's low attrition rate was similar to Mohr et al. (2008) study, which indicated that attrition rates are reduced when intervention is provided via the telephone instead of in person.

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Study's strengths and limitations

The current study had a number of strengths. The study's strengths consist of the following: (1) the use of randomized control design; (2) the utilization of a cost-effective accessible brief telephone-based IPT intervention; and (3) the inclusion of the EDPS's pretest scores as a covariate due to its potential effect on the depressive symptoms score and because it also differed significantly between the two study. On the other hand, the study had a number of limitations. First, the generalizability of the findings is limited to pregnant women who suffer from depressive symptoms, attributable to the relatively strict inclusion and exclusion criteria, which is common when using a RCT design. Second, the women's depressive symptom levels (pretest and posttest) were measured using a self-report questionnaire, thus, the results of the study might be influenced by social desirability responses, where the women might have provided responses that were congruent with prevailing social values to avoid stigma. Third, since the posttest of depressive symptoms only occurred at the end of treatment, this might have resulted in an intervention effect bias as the measurement was placed at the treatment maximum effect. Fourth, because there was no follow-up test after the cessation of treatment, it may be difficult to estimate how long the benefits of brief IPT lasted and whether the antepartum brief IPT is still effective in postpartum depressive symptoms beyond the duration of the study. Thus, larger longitudinal studies might be beneficial in supporting the widespread use of telephone-based IPT among pregnant women in Jordan. Finally, given that the data were collected from a single setting, it only included participants from urban areas. As a result, the findings of the study might be difficult to generalize to all pregnant women in Jordan.

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Implications

The study's findings have multiple implications that can help inform practice, policy, education, and future research. In regard to practice, midwives and general nurses working with pregnant women may benefit from receiving training on how to identify and screen all pregnant women for antenatal depressive symptoms given the high prevalence rate in Jordan. In addition, midwives and general nurses should be trained in basic psycho-educational counseling techniques to enable them to provide brief supportive care effective in reducing the risk of depression in this population. However, women with severe depression or at-risk of self-harm should be referred to psychiatric mental health nurses for more specialized care. Hence, policymakers should make psychotherapists available and accessible in antenatal care units and ensure that staff have adequate training via continuing **education programs** to screen for antenatal depressive symptoms. In terms of education, basic foundational educational training of psycho-educational counseling techniques (related to assessment of antenatal depressive symptoms) should be made available to midwives and general nurses in order to equip them with the essential knowledge and skills necessary to screen for antenatal depressive symptoms among pregnant women, provide basic supportive care, and refer more severe depression cases to specialized care.

The current study can be extended by conducting larger scale studies that **examine** the effect of brief IPT on antenatal depressive symptoms. In addition, qualitative studies should be conducted to explore how the participants felt about the intervention, and at what point the women started to feel better, as well as suggest ways to further improve the IPT brief intervention. Further research is needed to compare the usual antenatal education classes with IPT in order to identify the cost-effectiveness of both approaches. A cost-effectiveness analysis

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of the intervention could also be conducted. Finally, it is important to conduct a longitudinal study to examine the longer-term effect of IPT on antenatal depressive symptoms and maybe subsequent impact **on the prevention of postpartum depression.**

CONCLUSION

Pregnant women are regarded as a vulnerable population in need of every possible form of assistance to make their pregnancy experience a safe and joyful one. This study found that telephone-based IPT was effective in reducing depressive symptoms among pregnant Jordanian women. Thus, women who receive telephone based IPT sessions **might be** more likely to remain engaged with such an intervention. The finding of the current study can provide the basis for larger studies that utilize telephone-based IPT to address antenatal depressive symptoms among pregnant women in developing countries such as Jordan, which could benefit from a relatively low-cost more accessible brief IPT treatment.

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References

- Abuidhail, J., & Abujilban, S. (2014). Characteristics of Jordanian depressed pregnant women: a comparison study. *Journal of Psychiatric & Mental Health Nursing, 21*(7), 573-579. <https://doi.org/10.1111/jpm.12125>
- Abujilban, S., Mrayan, L., Al-Obeisat, S., Tanash, M., Sinclair, M., & Kernohan, W. G. (2022). Factors associated with antenatal depression in the Kingdom of Jordan during the COVID-19 pandemic. *PLOS Global Public Health, 2*(2), e0000194. <https://doi.org/10.1371/journal.pgph.0000194>
- Abujilban, S. K., Abuidhail, J., Al-Modallal, H., Hamaideh, S., & Mosemli, O. (2014). Predictors of antenatal depression among Jordanian pregnant women in their third trimester. *Health Care for Women International, 35*(2), 200-215. <https://doi.org/10.1080/07399332.2013.817411>
- Andersson, L., Sundstrom-Poromaa, I., Wulff, M., Astrom, M., & Bixo, M. (2004). Implications of antenatal depression and anxiety for obstetric outcome. *Obstetrics & Gynecology, 104*(3), 467-476. <https://doi.org/10.1097/01.AOG.0000135277.04565.e9> 104/3/467 [pii]
- Ban, L., Gibson, J. E., West, J., & Tata, L. J. (2010). Association between perinatal depression in mothers and the risk of childhood infections in offspring: a population-based cohort study. *BMC Public Health, 10*, 799. <https://doi.org/10.1186/1471-2458-10-799>
- Bandoli, G., Chambers, C. D., Wells, A., & Palmsten, K. (2020). Prenatal Antidepressant Use and Risk of Adverse Neonatal Outcomes. *Pediatrics, 146*(1). <https://doi.org/10.1542/peds.2019-2493>

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- Battle, C. L., Uebelacker, L. A., & Magee, S. R. (2012). Patient-centered care for antenatal depression. *American Journal of Obstetrics & Gynecology*, *207*(5), e10-11; author reply e11. [https://doi.org/S0002-9378\(12\)00716-8](https://doi.org/S0002-9378(12)00716-8) [pii] 10.1016/j.ajog.2012.06.062
- Biaggi, A., Conroy, S., Pawlby, S., & Pariante, C. M. (2016). Identifying the women at risk of antenatal anxiety and depression: A systematic review. *Journal of Affective Disorders*, *191*, 62-77. <https://doi.org/10.1016/j.jad.2015.11.014>
- Clark, C. J., Bloom, D. E., Hill, A. G., & Silverman, J. G. (2009). Prevalence estimate of intimate partner violence in Jordan. *Eastern Mediterranean Health Journal*, *15*(4), 880-889.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20187539
- Cox, J., Holden, J., & Sagovsky, R. (1987). Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry*, *150*, 782-786.
- Dadi, A. F., Miller, E. R., Bisetegn, T. A., & Mwanri, L. (2020). Global burden of antenatal depression and its association with adverse birth outcomes: an umbrella review. *BMC Public Health*, *20*(1), 173. <https://doi.org/10.1186/s12889-020-8293-9>
- Dennis, C. L., Ravitz, P., Grigoriadis, S., Jovellanos, M., Hodnett, E., Ross, L., & Zupancic, J. (2012). The effect of telephone-based interpersonal psychotherapy for the treatment of postpartum depression: study protocol for a randomized controlled trial. *Trials*, *13*, 38. <https://doi.org/10.1186/1745-6215-13-38>

Running head: INTERPERSONAL PSYCHOTHERAPY ANTENATAL DEPRESSIVE SYMPTOMS

Department-of-Statistics[Jordan], & ICF-Macro. (2010). *Jordan Population and Family Health Survey 2009*.

Department of Statistics(DOS), & ICF. (2019). *Jordan Population and Family and Health Survey 2017-18*. (J. Amman, and Rockville, Maryland, USA: DOS and ICF., Ed.)
<https://dhsprogram.com/pubs/pdf/FR346/FR346.pdf>

Diav-Citrin, O., & Ornoy, A. (2012). Selective serotonin reuptake inhibitors in human pregnancy: to treat or not to treat? *International Journal of Gynecology & Obstetrics*, 2012, 698947. <https://doi.org/10.1155/2012/698947>

Domingues, R. R., Fricke, H. P., Sheftel, C. M., Bell, A. M., Sartori, L. C., Manuel, R. S. J., Krajco, C. J., Wiltbank, M. C., & Hernandez, L. L. (2022). Effect of Low and High Doses of Two Selective Serotonin Reuptake Inhibitors on Pregnancy Outcomes and Neonatal Mortality. *Toxics*, 10(1). <https://doi.org/10.3390/toxics10010011>

Dong, Y., & Peng, C.-Y. J. (2013). Principled missing data methods for researchers. *SpringerPlus*, 2(1), 222. <https://doi.org/10.1186/2193-1801-2-222>

Gausia, K., Fisher, C., Ali, M., & Oosthuizen, J. (2009). Antenatal depression and suicidal ideation among rural Bangladeshi women: a community-based study. *Archives of Women's Mental Health*, 12(5), 351-358. <https://doi.org/10.1007/s00737-009-0080-7>

Goodman, S. H. (2012). Antenatal depression associated with increased risk of offspring maltreatment and psychopathology. *Evidence-Based Mental Health*, 15(1), 7.
<https://doi.org/ebmental-2011-100333> [pii]10.1136/ebmental-2011-100333

Running head: INTERPERSONAL PSYCHOTHERAPY ANTENATAL DEPRESSIVE SYMPTOMS

- Grote, N. K., Swartz, H. A., Geibel, S. L., Zuckoff, A., Houck, P. R., & Frank, E. (2009). A randomized controlled trial of culturally relevant, brief interpersonal psychotherapy for perinatal depression. *Psychiatric Services, 60*(3), 313-321. <https://doi.org/60/3/313> [pii] 10.1176/appi.ps.60.3.313
- Hartley, M., Tomlinson, M., Greco, E., Comulada, W. S., Stewart, J., le Roux, I., Mbewu, N., & Rotheram-Borus, M. J. (2011). Depressed mood in pregnancy: prevalence and correlates in two Cape Town peri-urban settlements. *Reproductive Health, 8*, 9. <https://doi.org/1742-4755-8-9> [pii] 10.1186/1742-4755-8-9
- Hay, D. F., Pawlby, S., Waters, C. S., Perra, O., & Sharp, D. (2010). Mothers' antenatal depression and their children's antisocial outcomes. *Child Development, 81*(1), 149-165. <https://doi.org/CDEV1386> [pii] 10.1111/j.1467-8624.2009.01386.x
- Hayes, L. J., Goodman, S. H., & Carlson, E. (2012). Maternal antenatal depression and infant disorganized attachment at 12 months. *Attachment & Human Development, 15*(2), 133-153. <https://doi.org/10.1080/14616734.2013.743256>
- Kim, D. R., Hantsoo, L., Thase, M. E., Sammel, M., & Epperson, C. N. (2014). Computer-assisted cognitive behavioral therapy for pregnant women with major depressive disorder. *Journal of Women's Health (Larchmt), 23*(10), 842-848. <https://doi.org/10.1089/jwh.2014.4867>
- Kim, D. R., Sockol, L., Barber, J. P., Moseley, M., Lamprou, L., Rickels, K., O'Reardon, J. P., & Epperson, C. N. (2011). A survey of patient acceptability of repetitive transcranial magnetic stimulation (TMS) during pregnancy. *Journal of Affective Disorders, 129*(1-3), 385-390. [https://doi.org/S0165-0327\(10\)00563-X](https://doi.org/S0165-0327(10)00563-X) [pii] 10.1016/j.jad.2010.08.027

Running head: INTERPERSONAL PSYCHOTHERAPY ANTENATAL DEPRESSIVE SYMPTOMS

- Kim, H. W., & Jung, Y. Y. (2012). [Effects of antenatal depression and antenatal characteristics of pregnant women on birth outcomes: a prospective cohort study]. *Journal of Korean Academy of Nursing*, 42(4), 477-485. <https://doi.org/201208477> [pii] 10.4040/jkan.2012.42.4.477
- Lenze, S. N., & Potts, M. A. (2017). Brief Interpersonal Psychotherapy for depression during pregnancy in a low-income population: A randomized controlled trial. *Journal of Affective Disorders*, 210, 151-157. <https://doi.org/10.1016/j.jad.2016.12.029>
- Leung, S. S., & Lam, T. H. (2012). Group antenatal intervention to reduce perinatal stress and depressive symptoms related to intergenerational conflicts: a randomized controlled trial. *International Journal of Nursing Studies*, 49(11), 1391-1402. [https://doi.org/S0020-7489\(12\)00222-2](https://doi.org/S0020-7489(12)00222-2) [pii] 10.1016/j.ijnurstu.2012.06.014
- Levis, B., Negeri, Z., Sun, Y., Benedetti, A., Thombs, B. D., & Group, D. E. S. D. E. (2020). Accuracy of the Edinburgh Postnatal Depression Scale (EPDS) for screening to detect major depression among pregnant and postpartum women: systematic review and meta-analysis of individual participant data. *BMJ*, 371, m4022. <https://doi.org/10.1136/bmj.m4022>
- Lin, I. H., Huang, C. Y., Chou, S. H., & Shih, C. L. (2022). Efficacy of Prenatal Yoga in the Treatment of Depression and Anxiety during Pregnancy: A Systematic Review and Meta-Analysis. *International Journal of Environmental Research & Public Health*, 19(9). <https://doi.org/10.3390/ijerph19095368>
- Madley-Dowd, P., Hughes, R., Tilling, K., & Heron, J. (2019). The proportion of missing data should not be used to guide decisions on multiple imputation. *Journal of Clinical Epidemiology*, 110, 63-73. <https://doi.org/10.1016/j.jclinepi.2019.02.016>

Running head: INTERPERSONAL PSYCHOTHERAPY ANTENATAL DEPRESSIVE SYMPTOMS

- Manikkam, L., & Burns, J. K. (2013). Antenatal depression and its risk factors: an urban prevalence study in KwaZulu-Natal. *South African Medical Journal*, *102*(12), 940-944. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=23498042
- Miller, L., Gur, M., Shanok, A., & Weissman, M. (2008). Interpersonal psychotherapy with pregnant adolescents: two pilot studies. *Journal of Child Psychology and Psychiatry*, *49*(7), 733-742. <https://doi.org/JCPP1890> [pii] 10.1111/j.1469-7610.2008.01890.x
- MOH. (2011). *Ministry of Health Annual Statistical Book 2011* MOH. http://www.moh.gov.jo/MOH/Files/Publication/PDF2011_1.pdf
- Mohammad, K. I., Abu Awad, D., Creedy, D. K., & Gamble, J. (2018). Postpartum depression symptoms among Syrian refugee women living in Jordan. *Research in Nursing & Health*, *41*(6), 519-524. <https://doi.org/10.1002/nur.21919>
- Mohammad, K. I., Gamble, J., & Creedy, D. K. (2011). Prevalence and factors associated with the development of antenatal and postnatal depression among Jordanian women. *Midwifery*, *27*(6), e238-245. [https://doi.org/S0266-6138\(10\)00169-5](https://doi.org/S0266-6138(10)00169-5) [pii] . 10.1016/j.midw.2010.10.008
- Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gotzsche, P. C., Devereaux, P. J., Elbourne, D., Egger, M., Altman, D. G., & Consort. (2012). CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *International Journal of Surgery*, *10*(1), 28-55. <https://doi.org/10.1016/j.ijssu.2011.10.001>

Running head: INTERPERSONAL PSYCHOTHERAPY ANTENATAL DEPRESSIVE SYMPTOMS

Mohr, D. C., Vella, L., Hart, S., Heckman, T., & Simon, G. (2008). The Effect of Telephone-Administered Psychotherapy on Symptoms of Depression and Attrition: A Meta-Analysis. *Clinical Psychology: Science and Practice, 15*(3), 243-253.

<https://doi.org/10.1111/j.1468-2850.2008.00134.x>

O'Mahen, H., Himle, J. A., Fedock, G., Henshaw, E., & Flynn, H. (2013). A pilot randomized controlled trial of cognitive behavioral therapy for perinatal depression adapted for women with low incomes. *Depression & Anxiety, 30*(7), 679-687.

<https://doi.org/10.1002/da.22050>

Ormsby, S. M., Smith, C. A., Dahlen, H. G., & Hay, P. J. (2020). The feasibility of acupuncture as an adjunct intervention for antenatal depression: a pragmatic randomised controlled trial. *Journal of Affective Disorders, 275*, 82-93.

<https://doi.org/https://doi.org/10.1016/j.jad.2020.05.089>

Polit, D. F., & Beck, C. T. (Eds.). (2011). *Nursing research: generating and assessing evidence for nursing practice* (Ninth ed.). Lippincott Williams & Wilkins.

Redshaw, M., & Henderson, J. (2013). From antenatal to postnatal depression: associated factors and mitigating influences. *Journal of Women's Health (Larchmt), 22*(6), 518-525.

<https://doi.org/10.1089/jwh.2012.4152>

Smith, M. V., Shao, L., Howell, H., Lin, H., & Yonkers, K. A. (2011). Perinatal depression and birth outcomes in a Healthy Start project. *Maternal and Child Health Journal, 15*(3), 401-409. <https://doi.org/10.1007/s10995-010-0595-6>

Sockol, L. E., Epperson, C. N., & Barber, J. P. (2011). A meta-analysis of treatments for perinatal depression. *Clinical Psychology Review, 31*(5), 839-849. [https://doi.org/S0272-7358\(11\)00057-2](https://doi.org/S0272-7358(11)00057-2) [pii] 10.1016/j.cpr.2011.03.009

[10.1016/j.cpr.2011.03.009](https://doi.org/10.1016/j.cpr.2011.03.009)

Running head: INTERPERSONAL PSYCHOTHERAPY ANTENATAL DEPRESSIVE SYMPTOMS

- Spinelli, M. G., & Endicott, J. (2003). Controlled clinical trial of interpersonal psychotherapy versus parenting education program for depressed pregnant women. *The American Journal of Psychiatry*, *160*(3), 555-562.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12611838
- Spinelli, M. G., Endicott, J., Leon, A. C., Goetz, R. R., Kalish, R. B., Brustman, L. E., Carmona, Y. R., Meyreles, Q., Vega, M., & Schulick, J. L. (2013). A controlled clinical treatment trial of interpersonal psychotherapy for depressed pregnant women at 3 New York City sites. *The Journal of Clinical Psychiatry*, *74*(4), 393-399.
<https://doi.org/10.4088/JCP.12m07909>
- Stuart, S., & Koleva, H. (2014). Psychological treatments for perinatal depression. *Best Practice & Research Clinical Obstetrics & Gynaecology*, *28*(1), 61-70. [https://doi.org/S1521-6934\(13\)00135-1](https://doi.org/S1521-6934(13)00135-1) [pii] 10.1016/j.bpobgyn.2013.09.004
- Swanson, L. M., Flynn, H. A., Wilburn, K., Marcus, S., & Armitage, R. (2010). Maternal mood and sleep in children of women at risk for perinatal depression. *Archives of Women's Mental Health*, *13*(6), 531-534. <https://doi.org/10.1007/s00737-010-0177-z>
- Weissman, M. M., Markowitz, J. C., & Klerman, G. L. (2000). *Comprehensive Guide to Interpersonal Psychotherapy*. Basic Books.
- Zejnnullahu, V. A., Ukella-Lleshi, D., Zejnnullahu, V. A., Miftari, E., & Govori, V. (2021). Prevalence of postpartum depression at the clinic for obstetrics and gynecology in Kosovo teaching hospital: Demographic, obstetric and psychosocial risk factors. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *256*, 215-220.
<https://doi.org/10.1016/j.ejogrb.2020.11.025>

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Table 1.

Telephone-based interpersonal psychotherapy intervention structure and content provided to depressed pregnant women with symptoms of depression in the intervention study arm

Phase	Session no. (duration)	Session content
Initial phase “pre-therapy orientation”	1 (30 min)	<ol style="list-style-type: none"> 1. Orient and explain the therapy process and structure 2. Enter into contract for therapy 3. Identify goals and create treatment outlines 4. Discuss with the participant the expectations associated with the therapy sessions, e.g., attendance, active participation
Intermediate phase	2- 5 (30 min each)	<ol style="list-style-type: none"> 1. Collecting information and making a comprehensive assessment about the initial problem related to participant’s interpersonal context and decide on the focus of the therapy 2. Review and evaluate the participant’s pattern and current relationships 3. Further clarification

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4. Linking mood to interpersonal problem areas
 5. Identify events in the participant's life that lead to depression
 6. Identify the interpersonal context in which the problem presents itself, e.g., grief, role disputes, role transition, interpersonal deficit
 7. Apply the interpersonal psychotherapy techniques, i.e., clarification of feelings, expectations and roles in relationships, communication analysis, and decision analysis
 8. Highlight skills and strategies that are particularly useful
- | | | |
|---------------|--|--|
| Closing phase | 6 th and 7 th
30 min) | <ol style="list-style-type: none"> 1. Review the participant's course of depressive symptoms and how they have changed 2. Review changes in interpersonal functioning 3. Link these changes to improvement in the participant's mood 4. Discuss the end of treatment |
|---------------|--|--|
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Table 2

Sociodemographic characteristics of the participants by study group, showing no significant demographical differences between the two groups.

Demographic variable	Control group mean	Intervention group mean	<i>p</i>	Total
Age in years	28.8	29.2	0.7	29
Gestational age	31.3	31.3	0.9	31.3
Total household income	396	355	0.3	375.5
Number of years of education	11.5	11	0.4	11.3
No. of antenatal visits	9	8.4	0.5	8.7
Ultrasound	9	8.3	0.4	8.6
Gravida	4.5	4.7	0.7	4.6
Number of live children	2.3	2.7	0.8	2.6
No. of miscarriages	2.1	2.6	0.5	2.4
Hb level	10.7	10.5	0.5	10.6

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		<i>n</i>	%	<i>n</i>	%	<i>P</i>	Total	%
		<i>n</i>						
Employment								
status	Housewife	45	90	50	100		95	95
	Employed	5	10	0	0	0.07	5	5
Husband's employment status	No	2	4	1	2		3	3
	Yes	48	98	49	96	1	97	79
Husband's education	No education	0	4	3	6		3	3
	Elementary	3	6	6	12		9	9
	Middle school	15	30	12	24		27	27
	Secondary	23	46	25	50		48	48
	Bachelor	9	18	4	8	0.1	13	13
	Health problems during pregnancy	No	37	74	40	80		77
	Yes	13	26	10	20	0.6	20	20

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Table 3

The difference in EPD's mean score among pregnant women pre-test and posttest by study group.

Outcome Variable	Control Group (n = 50)			Intervention Group (n = 50)			t-test for pretest	p- valu e
	Test	Unadjusted Mean (SD)	Adjusted Mean (SE)	Test	Unadjusted mean (SD)	Adjusted Mean (SE)		
EPDS	Pretest	17.82 (2.79)		Pretest	19.34 (3.59)		2.36	0.04
	Posttest	16.42 (4.35)	16.43 (0.74)	Posttest	8.88 (5.82)	8.87 (0.74)		0.00
								0**

Note. Variables included obtaining the adjusted means: study group, and the woman's pre-the Edinburgh Postnatal Depression Scale (EPDS); Control group= received routine care; Intervention group= received telephone-based intervention sessions; SD= standard deviation; SE= standard error; ** $p < 0.01$; * $p < 0.05$.