The Effectiveness of Psychopharmacological Intervention versus Cognitive Behavioral Couple Therapy and their Combination in Perinatal Distressed Couples: A Randomized Clinical Trial

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Abstract

Perinatal distress as manifested in the symptomology of Major Depressive Disorder and Generalized Anxiety Disorder in mothers has detrimental effects on foetus and infants. Keeping in consideration the well-being of foetus and infant, the present study has focused on provision of treatment to the screened high-risk distresses mothers along with inclusion of fathers visiting obstetrics/gynaecology wards in the hospitals. The present randomized clinical trial will be carried out on nth participants (Nth couples), recruited from the Maternity Clinic, Islamabad and Qamar Maternity Hospital, Gujar Khan, Pakistan. Randomization will be carried out in this completely randomized experimental research design. The multi-arms parallel group trial will be conceded. The participants will be randomly allocated either to intervention groups or waitlist control groups with the use of online random number generator calculator. The five intervention arms will be Psychopharmacological intervention, Cognitive Behavioral Couple Therapy (CBCT), CBCT with Zikr, combination of psychopharmacology with CBCT, and combination of psychopharmacology with CBCT along with Zikr. The medicines will be prescribed by a gynaecologist after thorough evaluation of risk and benefits. Ten therapeutic sessions (60 minutes) by the investigator will be administered in group. The waitlist control group will receive either a placebo or no intervention which implies that they will carry out routine gynaecological check-ups. A sum of scores obtained with Major Depressive Disorder Subscale (MDDS) and Generalized Anxiety Disorder Subscale (GADS) of Parental Perinatal Distress Scale (PPDS) will used to assess levels of perinatal depression and perinatal anxiety, collectively named perinatal distress in couples before and after intervention. In addition, Urdu versions of Dyadic Coping Inventory (DCI), Multidimensional Scale for Perceived Social Support (MSPSS), Flourishing Scale (FS), and World Health Organization Quality of Life Scale-WHOQOL-BREF will be used to assess coping strategies, social support, wellbeing, and perceived quality of life at pre-test and post-test. Based on adjustment of baseline pre-test total scores for distress (anxiety and depression) and monthly income, ANCOVA will be applied to assess the impact after treatment for five intervention groups as compared to two control group. It will be fruitful to deliver mental health services in antenatal and postnatal periods for alleviation of mental health and prevention of psychopathological disorders in high-risk couples while screening visitors coming in obstetrics and gynaecological wards for routine check-ups in Pakistan.

Background

The mental disorders such as depression, anxiety, bipolar disorder, and psychosis play significant role in influencing mother's and baby's health during pregnancy and postpartum [1]. Child's cognitive and physical development during pregnancy and after delivery is effected by mother's mental health [2-4]. These researches signify the importance of early screening and efficacious management for the symptoms of mania, anxiety, and depression in women during perinatal women [1]. The cognitive-behavioural model comprehends the experiences of depression in reciprocal interaction between thoughts, emotions, and behaviours in a peculiar context thereby elaborating their etiopathogenetic contributions. It further expounds these interpretations into the development of clinically effective techniques aimed at reduction of the problematic expression of the symptoms [5]. This model is also empirically effective for treating anxiety disorders [6]. The cognitive and behavioural techniques have long-term effects in reducing the levels of depression and the anxiety disorders [7]. Nevertheless, fathers suffering with depression and anxiety during perinatal period receive reduction in the symptoms by use of cognitive behavioral therapy in group [8].

The prevalence for perinatal depression ranged between 10% and 20% for women impacting not only them but also their husbands and children [9]. A high prevalence rate 29.2% and 24.4% is observed for antenatal and postnatal anxiety in women [10]. Paternal perinatal anxiety was found to be 10.69% [11] whereas average paternal perinatal depression was reported to be 9.25% [12]. Thus, treatment plan has to be inclusive to the fathers as well as to the mothers for better wellbeing of foetus and baby. Interventions with psychoeducation, communication training, and behavioral activation benefit women when husbands are involved in the therapeutic treatment [9]. Therefore, gaps exist in understanding and treatment of perinatal depression and perinatal anxiety in women [13]. The effective treatment and prevention of postpartum depression included studies based on randomised controlled trials with investigation of psychosocial factors and counselling interventions. The randomized controlled trials used lowest effective dose for management of depression and anxiety symptoms during antenatal and postnatal period after conducting a risk-benefit analyses based on individual cases for treatment. For future trial researches, it has been recommended that involvement of fathers along with mothers and focus on economic constraints in low income settings could yield beneficial results in provision of mental health facilities [14].

Cognitive Behavioral Couple Therapy (CBCT) is the offshoot of Cognitive Behavior Therapy (CBT); the amalgam in the cognitive- and behavior therapies to focus on dysfunctional

relationships between husband and wife. Healthy functioning is practiced by structure of the therapy process, assessment and intervention plan with focus on goal setting by a therapist to eliminate distress and enhance wellness and satisfaction [15-16]. The third wave in couple therapy showed integration of meditation, religiosity and spirituality for the improvement of the quality of relationship between husband and wife [17-19]. Recently, empirical evidences of randomized controlled trial in meditation have been found to be effective improving electroencephalograph (EEG) in brain waves for the reduction of psychological distress [20]. The present study has focused on application of CBCT because Patterson (2017) [21] has found CBCT to be empirically sound for providing experimentation based evidences than any other therapeutic intervention used with couples. In order to assess efficacy of CBCT among perinatal couples, a randomized clinical trial will be used. According to James, Rao, and Granger [22], randomized clinical trials are empirically proven methodology of reliably controlling the confounding variables and presenting a plausible association between selection of treatment option and well-being outcome. The Perinatal Distress Model signifies the crucial role played by socio-cultural traditional explanations for distress in pregnancy and after birth for women in Pakistan [23]. Therefore, one cannot ignore the role of socio-cultural practices for healing in perinatal women. Zikr is considered instrumental in provision of improved mental and physical health among Muslims [24-25]. The word Zikr is interchangeably used with word of medication or more precisely Islamic meditation or mindfulness.

Meditation is defined as the individual's ability "to focus their attention on a single object, such as an image or a mantra" [26]. Mediation and mindfulness is linked and considered to be the synonyms of one another that play a crucial role in decline of psychological distress [27-30]. "Mindfulness has been described as a practice of learning to focus attention on moment-by-moment experience with an attitude of curiosity, openness, and acceptance" [31] (Marchand, 2012, p. 233). Therefore, the elements of meditation or mindfulness implied focus on experience, sensation, image, mantra, thought and gradual enhancement of that focus of attention, transforming into the practice of concentration, eliminating the thoughts and gaining relaxation. The mindfulness or more precisely meditation in Pakistani culture is visible in religio-spiritual context of Islam.

Muraqabah in Islam is conceptually akin to meditation or mindfulness technique, except they differed in use of Zikr or mantras [32-33]. The meanings of mediation in Islam are diverse ranging from focus on remembrance of God, Dhikr/Zikr, by vocalization of Quranic verses, or Divine Names to formal ritualized manner of performing prayers five times a day [34]. Zikr, remembrance of God, has been found to be effective in reduction of distress, pain and suffering

in various physical and psychological disorders [35-38]. The present research has focused on use of Professor Ahmed Rafique Akhtar's approach towards Zikr, based on two Quranic verses: Translation: "Remember Allah like your remembrance of your fathers or with greater remembrance" (Al Quran, Surah Bakarah, Verse 200). Translation: "And when I am ill, it is He who cures me" (Al Quran, Surah Shu'ara, Verse 80).

In order to make Zikr one's habit, it is necessary to initiate the recitation without concentration because in this way one remember Allah as he tries to remember his beloved relatives and significant others with affection and nostalgia. Ones it become your habitual memorization and one attain regularity in it; it can be imparted to others. The Zikr can be recited without ablution (wozu), through tongue, casually, informally, performing various tasks, such as watching television, listening to music, and talking etc. The imparting of Zikr is exclusively contingent on the values of the individuals. It is neither recited on someone else behalf nor without personal willingness. It is intended to be recited regularly for the sake of God only not for any worldly gain or aim. The term Zikr is used instead of meditation because there is no condition of focused attention or concentration in the remembrance of God through His Names especially Ya Salam (The Peace Giver), Ya Momin (The Faith Giver), Ya Allah (300 times per day); Ya Rehman (The Merciful), Ya Raheem (The Compassionate), Ya Kareem (The Generous) (300 times per day); Lahaolawala quwata illah billah (There is no might nor power except with Allah, 300 times per day) to name a few. The quantity for recitation is adjustable according to the person's capacities. Care must be taken in recitation of either Ya Salam or Ya Momin. The names starting with S should avoid recitation of Ya Momin and the names starting with M should refrain from oration of ration of a Salam [39-40]. Either Ya Salam (100 times) or Ya Momin (100 times) and Ya Rehman (100 times) along with Lahaolawala quwata illah billah (100 times) and Ayat Kareema (40 times) were found effective in reducing dysthymic symptomology in a patient when imparted in junction to CBT [41]. Numerous researches have posited the efficacy of Zikr in reducing perinatal depression and perinatal anxiety [42-44].

The values and preferences of the clients have to be considered and respected while providing the treatment with cognitive behavior therapy [45]. This basic principle in Beck's Approach to Cognitive Behavior Therapy, undermines the bifurcations in CBT practice by renaming it as "Religious Cognitive-Behavior Therapy" [46-47], "Secular and Religious versions of Cognitive Behavior Therapy" [48], "Religious and Nonreligious Cognitive-Behavioral Therapy" [49], "Religion-Adapted Cognitive Behavioral Therapy" [50], "Religious vs. conventional cognitive behavioral therapy" [51] and [41, 52].

A systematic review of ten randomized controlled trials aimed at comparison of combined treatment of medicines and CBT with CBT alone for broad spectrum anxiety disorders was carried out. The findings posited non superior effectiveness of combined CBT with medicine treatment and CBT monotherapy treatment in anxiety disorders with respect to effect size [53]. Similar findings in another review indicated that combination of anxiolytics and CBT for different kinds of anxiety disorders are not better than monotherapy of medicine and CBT [54]. However, meta-analysis of psychopharmacological and psychological intervention (specifically CBT) showed significant improvement in perinatal depression with effect size Hedges' g 0.65 [55]. Additional meta-analyses revealed effectivity of CBT [56-58] and antidepressants [59] in perinatal depressed women. But placebo controlled trials did not reveal efficacious differences for medications in depressed women during antenatal and postpartum period [60-61].

In Pakistan, scarce randomized controlled trials (RCT) have been carried out to reduce prenatal anxiety [62] and perinatal depression [63-64] in women via psychotherapeutic interventions. However, a few researches have reported about the effectivity of Zikr in decreasing antenatal depression and anxiety in pregnant women in Indonesia [65-66]. Therefore, a gap existed in evaluation of efficacy of psychopharmacological approach injunction with psychological intervention and Zikr for reduction of symptomology of perinatal distress in women and men (spouse). Hence, the primary objective of this research was to evaluate the impact of treatment with medication, CBCT (conditions: with or without Zikr), and their combination to decrease symptoms of distress (depression and anxiety) assessed by using the Major Depressive Disorder Subscale and Generalized Anxiety Subscale of Parental Perinatal Distress Scale in the fourth month and onward pregnancy till one year after childbirth in high-risk couples between intervention and control groups (primary outcome).

Objectives of the Study

The primary objective of the present study will be:

- To evaluate effectivity of psychopharmacological treatment, CBCT (with or without Zikr), and combined medicine-CBCT (with or without Zikr) interventions be in reducing symptoms of distress and improving quality of life, social support, wellbeing, and coping strategies among couples during the perinatal period at the post-test level as compared to the waitlist control group in the high risk couples for perinatal distress.

The secondary objective of the present study will be:

- To report occurrence of side-effects after the use of psychotropic medications in in the high risk couples for perinatal distress.

- To report occurrence of any adverse events after the use of psychotropic medications in in the high risk couples for perinatal distress.

Hypotheses of the Study

The presence of mix findings for efficacy of different interventions instigated sequential superiority-equivalence approach in hypotheses. The primary hypotheses based on the superiority trial approach of the study will be:

- There will be significant differences in psychopharmacology on total scores of perinatal distress between the experimental and wait list-control groups.
- There will be significant differences in CBCT on total scores of dyadic coping strategies between the experimental and wait list-control group.
- There will be significant differences in CBCT with Zikr on total scores of perceived social support between the experimental and wait list-control groups.
- There will be significant differences for combined psychopharmacology, and CBT with Zikr on total scores of wellbeing between experimental and wait list-control group.
- There will be significant differences for combined psychopharmacology, and CBT without Zikr) on total scores of perceived quality of life between experimental and wait list-control group.

The secondary hypothesis based on the equivalence trial approach of the present study will be:

- Combined intervention with psychopharmacology and cognitive behavioural therapy (with or without Zikr) will not be more effective than only psychopharmacology and only CBCT in treating distress in intervention group.

Methodology

The study was approved by Institutional Review Board (IRB), University of Gujrat, with reference no: UOG/ORIC/2022/393. After initial registration dated 26th June, 2023, the trial protocol was approved on 13th August, 2023 by ClinicalTrials.gov, reference no: NCT06001021, to start the enrolment and sampling. The research will take place from 15th August, 2023 to 30th September, 2023; with two follow-ups in October, 2023, each conducted after a two-week gap.

Study Design

The completely randomized design (CRD) is used to assign sample units to different treatment groups [67-69]. Each sample unit is considered uniform (all were selected at high risk with inclusion criteria) with respect to the presence of the perinatal distress. Therefore, the present

study will be multi-arm parallel group randomized trial [70-71]. The present double-blind randomized controlled clinical trial will contain five parallel arms of interventions and a waitlist control arm (conditions: either with administration of a placebo or no intervention). The participants and a research assistant will be blinded for allocation of the participants to the parallel arms for maintaining the principle of randomization.

The study design is sequential superiority-equivalence trial [72-73]. Superiority trial hypotheses apply statistical test to consider evidence for a treatment to be better than the control either with no treatment or with placebo. Equivalence trial hypotheses apply statistical test to exhibit that any two treatments are not too different in characteristics, and any limited differences are operationally defined in a clinical manner [74]. Recruitment will be carried out from 15th August, 2023 to 26th August, 2023 in a Maternity Clinic Islamabad and Qamar Maternity Hospital in Gujar Khan, Pakistan. The participants visiting obstetrics/gynaecological clinic, hospital will be identified via screening carried out by the investigator and the research assistant. They will be assessed according to the eligibility criteria and written informed consent will be sorted. The n% of participants fulfilling inclusion eligibility criteria and giving consent to take part in the study will be up taken strategically receiving recruitment to be randomized into intervention and control groups of the RCT.

Sample Size

The sample size will be calculated manually by using a formula [75]:

$$\frac{Z_{1-\alpha/2}^2\, p\,(1-p)}{d^2}$$

Where, $Z_{1-\alpha/2}$ is considered a standard normal variate; p is the expected proportion (prevalence) of perinatal distress in the population based on the study of Smythe et al., [76]; and d is the absolute error, decided by the researcher as 0.10 based on the suggestion by the experts [77-78]. The researcher has decided absolute error to be fixed at 0.10 due to lack of financial resources and economy of time.

The sample size calculated with above formula will be used and 7 participants will be considered for each arm. Since, the present study considers couples, for couples per arm of five intervention groups and one control group of RCT will be taken. Hence, it implies that 4 couples in each arm will be sufficient for the performance of the RCT to evaluate effectivity of CBCT in the main study. Nevertheless, a sample size of 15 participants in each arm is considered based on statistical considerations of sample size in randomized controlled trials [79]. Therefore, five intervention groups and one control arm necessitates recruitment of a total of 90 participants in a

study. In addition, 10% additional sample size is kept in the present study to avoid issues of loss of the participants in post-test assessment and follow-ups [80-81]. Formula for adjusted sample size with 10% dropout rate [82] is given below:

Adjusted Sample Size = calculated sample size divided by (1-dropout rate)

The adjusted sample size is 8 participants. Since, the present research will be conducted on the couples, 4 couples (8 participants) will be added to get adjusted sample size with 10% dropout forecast to actual sample size calculated for each arm that is four couples (8 participants).
Conclusively, 16 participants will be recruited with randomization in a present clinical trial in each five arms of intervention group (Psychopharmacological intervention arm; CBCT without Zikr arm; CBCT with Zikr arm; combined psychopharmacological intervention with CBCT without Zikr arm; and combined psychopharmacological intervention with CBCT with Zikr arm) and a control group (either with placebo arm or no intervention arm). The sample size will be of 96 participants (48 couples) in present RCT.

Inclusion/Exclusion Criteria

Inclusion Criteria for the participants will focus on: couples age range 19 to 45 years; fourth month of pregnancy till the seventh month of the antenatal period, One week after delivery/birth till one year of a child in the postnatal period; screened by Major Depressive Disorder Subscale and Generalized Anxiety Disorder Subscale of Parental Perinatal Distress Scale as high-risk couples, with perinatal depression (cut-off score 29 to 42) and perinatal anxiety (cut-off score 17 to 24), and their comorbidity (cut-off score ≥ 40 and ≥ 20 on both subscales respectively; total sum of scores on both MDDS and GADS ≥45 for high risk perinatal distress; Dose requirements in any one or in combination of the antidepressant and/or anxiolytic, such as escitalopram (5-10 mg), sertraline (12.5-25 mg), and/or alprazolam (0.25-0.50 mg) per day; Wives accompanied by their husbands; husband is earning monthly income; couple is learned; Willingness to participate as a couple in the study; No physical disorder is present; No intellectual disability is present; no history of miscarriage or infant mortality in one year; no history of psychiatric disorder or psychotropic drug intakes. Exclusion Criteria will focus on: age range below 19 and above 45 years; unwilling couples or any one, to participate in the study; wife and/or couple is in an emergency; wife and/or couple has unstable mental health; wife accompanied by close relatives other than a spouse; wife in the first week of delivery; ; low score on either or both MDDS and GADS than inclusion criteria for high risk perinatal distress; dose requirements in any one of the antidepressant and/or anxiolytic, such as escitalopram (>10 mg), sertraline (>25 mg), and/or alprazolam (>0.50 mg) per day; husband is not earning monthly income and other family

members are the source of income; either wife or husband is illiterate; screened couples having psychotic features; screened couples either having suicidal ideation or manic/hypomanic features; couples either having diabetes or cardiovascular disorders; any intellectual, visual, or hearing disability present in either spouse of a couple; history of miscarriage or infant mortality in one year; history or presence of diagnosis with psychiatric disorder and/or psychotropic medicine intake.

Recruitment

Recruitment will be carried by the investigator along with a research assistant after screening nth women along with their husbands coming for their routine check-ups at a clinic, Islamabad and Qamar Maternity hospital, Gujar Khan with Major Depressive Disorder Subscale and Generalized Anxiety Disorder Subscale of Parental Perinatal Distress Scale. Written informed consent will be sorted. Intervention arms of CBCT (conditions: with or without Zikr) will be carried out in Islamabad whereas rest of the arms will be carried out in Gujar Khan. It will not be a multisite randomization due to lack of resources and unavailability of funds.

After going through the informed consent form, written consent was taken for participation in the study. A list of nth willing participants with preferred mode of treatment was prepared. The research assistant inquired the willing high-risk participants to select one of their preferred treatment modes out of the following:

a. Medications (antidepressants and/or anxiolytics).
b. Cognitive Behavioural Couple Therapy without Zikr.
c. Cognitive Behavioural Couple Therapy with Zikr.
d. Combination of medications and cognitive behavioral couple therapy without Zikr.
e. Combination of medications, cognitive behavioral therapy, with Zikr.

Randomization

However, the participants will be allocated to treatment group or control by random number generation via online calculator [83] by a research assistant to maintain the principle of randomization. They were not provided with their preferred mode of treatment until completion of the study. They will be briefed in the follow-ups about the study and will be given preferred mode of treatment on approval. This information will be recorded in the investigator's files with a random number assigned. A research assistant will be allowed to look at these files after completion of the research. Consultant gynaecologist and a research assistant will look after the couples for their physical concerns during the study participation. Participants will receive

psychopharmacological treatment according to the National Institute for Health and Care Excellence guidelines [84] by a consultant gynaecologist.

The couples in group 1 will be given medications or placebo for two weeks and/or for four weeks maximum by the consultant gynaecologist. In next two weeks, medication will be tapered off and eventually stopped. The couples in group 2 will be treated with ten CBCT sessions either with Zikr or without Zikr. The couples in group 3 will be provided with medication for two to four weeks and tapering off along with termination in two more weeks. They will also be provided with ten sessions of CBCT either with Zikr or without Zikr. The couples in group 4 will be given no intervention that is they carried out the routine gynaecological check-ups.

Allocation, Allocation Concealment, and Double-Blind in Trial

Allocation sequence in the list of nth participants was subjected to randomization [83]. Allocation concealment will be achieved by not letting the participants and research assistant know about the treatment or control arm. The intervention mode will be sealed in an envelope with a random number. A total of nth participants (Nth couples) were identified, screened and simple randomly allocated either to intervention group or control group by the research assistant [85, 86]. They will be assigned to parallel arms of either intervention (5 arms) or a control group by simple randomization through online calculator [83] with allocation ratio of 1:1 by the research assistant. The waitlist control group will be further divided into placebo receiving sub-group and no intervention or routine gynecological checkup receiving sub-group. Both the participants and the research assistant will not know about the allocation identity of the couples either to the treatment or control group.

The intervention group participants and waitlist control participants will be briefed about the study after completion and will be compensated with provision of their preferred mode of treatment. Thus, the participants and research assistant will be blinded to the nature of the treatment mode they will receive.

Intervention

After signed informed consent, the participants in CBCT (with or without Zikr) arm and combination of CBCT (with or without Zikr) with psychopharmacological arm will be provided with ten sessions (two sessions per week, each session 60 minutes of duration) in groups. The contents of all sessions (except session 4 and 5) for participants in condition with Zikr and without Zikr were same for 45 minutes. However, in the last 15 minutes of session 4 and 5, the participants with Zikr were imparted Zikr by the investigator whereas the participants without

Zikr carried out group discussion on philosophy of life, moderated by a research assistant. The contents of the sessions are briefly given as the following:

In the first session, rapport will be build and pre-test assessment will be carried out. In the second session, participants will be psycho-educated for perinatal period distress, couples' physical and mental health and impact on the fetus-infant, the prevalence of depression and anxiety, and the significance of identification. Progressive muscle relaxation exercises will be carried out along with deep breathing. Feedback on the session will be taken. In the third session, participants will be psycho-educated on the theoretical model of cognitive-behavioral couple therapy with some historical highlights and empirical standing. A thought log will be given for homework. Feedback for deep breathing and progressive muscle relaxation will be carried out. In the fourth, fifth, sixth, seventh, eighth, and ninth session, feedback will be taken on homework and session. Various techniques of Cognitive Behavioural Couple Therapy will be applied based on the nature and contents of identified precipitating, perpetuating, and present stressors. In addition, relevant techniques will be incorporated from other modalities with eclecticism. Tasbeeh in Zikr will be given to group 3 and group 5 who opted for it in the screening process. On the tenth visit, feedback on the session and homework will be taken. Post-test assessment will be done in the following two approaches Group 5 will be exposed to one of the two conditions.

However, after the completion of the research, the intervention group and waitlist group (control) will be briefed and will be delivered with an intervention mode of treatment of their choice as selected earlier.

Assessment Instruments

In a qualitative approach, the semi-structured interview schedule will be used to explore the present stressors, their expectations, and perceptions about the effectivity of treatments for perinatal distress among couples at pre-test and post-test assessment. In quantitative approach, five reliable and valid instruments will be used. The levels of perinatal depression and perinatal anxiety will be measured by Major Depressive Disorder Subscale and Generalized Anxiety Disorder Subscale of Parental Perinatal Distress Scale (PPDS), comprised of 14 and 8 items, with Cronbach's alpha reliability coefficients 0.89 and 0.82 respectively. The two subscales showed acceptable convergent, divergent, and discriminant validity. It is a Likert scale with "0" for "never" and "3" for "always" categories of response. The total scores for 22 items ranged from 0 to 66 with higher score indicating presence of high distress [87]. The levels of coping strategies will be measured by Urdu version [88] Dyadic Coping Inventory (DCI) comprised 37 items with 1 to 5 scoring categories. However, items 36 and 37 will not be included in the scoring as these are evaluative items. Scores for the remaining 35 items range from 35 to 175.

The cut-off score below 111 showed below average dyadic coping, scores between 111-145 showed normal dyadic coping range, score above 145 showed above average dyadic coping [89]. The levels of social support will be measured by Urdu version [90] Multidimensional Scale for Perceived Social Support (MSPSS) comprised 12 items with 1 to 7 scoring categories. Scores range from 12 to 84, with higher scores indicating higher levels of social support available for perinatal couples [91]. The levels of well-being will be measured by Urdu version [92] Flourishing Scale (FS) comprised 8 items with 1 to 7 scoring categories. Scores range from 8 to 56, with higher scores indicating better wellbeing in perinatal couples [93]. The levels of perceived quality in physical (7 items), psychological (6 items), social (3 items), and environmental (8 items) aspects of life were measured by Urdu version [94] World Health Organization Quality of Life-BREF (WHOQOL-BREF) comprised 26 items with 1 to 5 scoring categories. Item 1 and item 2 were not included in the scoring domains because these were evaluative items. Scores for physical aspect of life ranged from 7 to 35, 6 to 30 for psychological aspect, 3 to 20 for social, and 8 to 40 for environmental aspect of life. The higher scores indicate better quality in that particular domain of life in perinatal couples. In manual transformation of these raw scores obtained with WHOQOL-BREF to 0-20 and 0-100 scale have been given [95]. However, the investigator will use raw scores obtained in four subscales separately as domain wise comparison is recommended in the manual.

Discussion

In Pakistan, scarce randomized controlled trials have been conducted to investigate perinatal depression and anxiety in women [62-64]. However, survey research with cross-sectional design have been conducted in rural and urban areas of Punjab, to examine the association among social support, quality of life, wellbeing, and coping strategies with depression and anxiety during antenatal and postnatal period. A study was conducted to explore the maternal depression in rural areas of North Punjab and empirical evidence showed high social support resulted in lower major depressive symptoms in women during postnatal period [96]. Similarly, another research study reported inverse significant correlation of antenatal depression with perceived quality of life in women [97]. Likewise, prenatal anxiety related with obsessions and compulsions predicted wellbeing negatively in pregnant women [98]. Poor coping strategies significantly predicted high antenatal depression and anxiety in pregnant women [99]. To fill in the gap, the present randomized clinical trial will investigate the impact of intervention on perceived quality of life, social support, wellbeing and coping skills of high risk couples with perinatal distress.

The strength of the present study will be empirical exploration of impact of generic psychopharmacological intervention, CBCT (with or without Zikr), and combination of

psychopharmacology with CBCT (with or without Zikr) treatment in reducing perinatal distress (depression and anxiety) and improving perceived social support, wellbeing, quality of life, and coping strategies among the high risk screened couples for perinatal distress in Pakistan. The psychopharmacologic intervention will be used either with escitalopram, or sertraline, or alprazolam. The short-term use of the medications with preventive aim showed minor side-effects that subside with passage of time. The inclusion criteria with dose restriction alprazolam (0.25 to 0.50 mg/day), or escitalopram (5 to 10 mg/day), or sertraline (12.5 to 25 mg/day) is in safety limits with no reported adverse events in mothers during perinatal period according to the experts [100-102]. However, the present study will record and report occurrence of side effects and adverse events (if any) with the use of psychopharmacological intervention in screened high risk couples for perinatal distress, provided with medication by a gynaecologist after evaluation of risk and benefits for preventive purposes.

The current study is having certain limitations. Firstly, a complex research design (such as factorial, cross-over, cluster, multisite) in randomized clinical trial is not selected. Secondly, the sample size was small with 0.10 precision adjustments due to lack of financial resources and constraints of time duration for the completion of the present unfunded research project. Sample size with precision 0.05 must be increased in further experimental studies. A factorial design with main effect of escitalopram, sertraline, and alprazolam in a randomized controlled trial might be carried out to compare differential efficacy of drug used for reduction of the perinatal distress with screened high, medium, and low risk couples for preventive purposes. A block design with or without Zikr bifurcation can be added to medication. Further, High Performance Liquid Chromatograph (HPLC) could be used to monitor safety and harmless impact of psychotropic drugs after stoppage. A randomized block design might be applied to segregate couples based on gender, age, and monthly income. A multisite cluster randomized trial could be designed by inclusion of either metropolitan cities or rural villages of Punjab.

Conclusions

The findings will imply for placement of psychologists/clinical psychologists in gynaecological wards of the hospitals and clinics for timely screening, prevention, and treatment the women and their husbands for mental health during perinatal period. Training workshops may be conducted for gynaecologists to sensitize them towards the issue of psychopathologies and their appropriate identification, screening, referral, and management in antenatal and postnatal period for better maternal and paternal wellbeing.

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Duration of the Data Collection for RCT: 15th August, 2023 to 30th October, 2023.

Phase	**Date**
Recruitment: Initial screening, selection, informed consent, and randomization	15th August to August 26, 2023
Session 1: Pre-test Assessment	August 28, 2023
Session 2	August 31, 2023
Session 3	September 4, 2023
Session 4	September 7, 2023
Session 5	September 11, 2023
Session 6	September 14, 2023
Session 7	September 18, 2023
Session 8	September 21, 2023
Session 9	September 25, 2023
Session 10: Post-test Assessment	September 28, 2023
1st follow-up	October 14, 2023
2nd follow-up	October 28, 2023

Author's Contribution

SS contributed to conceptualization, methodology, data acquisition, data analysis, draft writing and review as per ICMJE criteria of authorship.

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