HHS Public Access

Author manuscript

Nat Med. Author manuscript; available in PMC 2024 April 30.

Published in final edited form as:

Nat Med. 2024 March ; 30(3): 675–682. doi:10.1038/s41591-024-02809-x.

Anxiety-focused cognitive behavioral therapy delivered by non-specialists to prevent postnatal depression: a randomized, phase 3 trial

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Abstract

Anxiety experienced by women during pregnancy is highly prevalent, especially in resource-poor settings, and strongly predicts postnatal common mental disorders (CMDs), anxiety and depression. We evaluated the effectiveness of an anxiety-focused early prenatal intervention on preventing postnatal CMDs. This study was a phase 3, two-arm, single-blind, randomized controlled trial conducted in Pakistan with women who were ≤22 weeks pregnant and had at least mild anxiety without clinical depression. Participants were randomized to the *Happy Mother-Healthy Baby (HMHB)* program, based on cognitive behavioral therapy, consisting of six one-on-one intervention sessions in pregnancy delivered by non-specialist providers, or to

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Author Contributions

P.J.S. conceptualized the study, drafted the original manuscript, contributed to the interpretation of results, and was the study's principal investigator. A.M. supervised the implementation of the study including data collection and all field activities, reviewed the manuscript and contributed to the interpretation of the results. J.P. performed the statistical analysis, drafted the results, reviewed the manuscript, and contributed to the interpretation of the results. N.A. led the development of the HMHB intervention, supervised its delivery, reviewed the manuscript and contributed to the interpretation of the results. A. Rowther contributed to the writing and editing of the manuscript. A.Z. managed the data, cleaned and curated the data and constructed the flow chart. A. Rahman conceptualized the study, assisted in supervision of the team, edited the manuscript, and contributed to the interpretation of the results. All authors approved the final manuscript.

Competing Interests Statement

The authors declare no competing interests.

Code Availability

Data structures, variables and variables names and relevant codebooks used for the statistical analyses have been uploaded to the NIMH Data Archives and are freely available to the public for use https://nda.nih.gov/.

enhanced care alone. The primary outcome was major depression, generalized anxiety disorder, or both at six-weeks after delivery. 755 women completed postnatal assessments (380 (50.3%), intervention arm; 375 (49.7%) enhanced-care arm). The primary outcomes were met. Examined jointly, we found 81% reduced odds of having either a Major Depressive Episode (MDE) or moderate-to-severe anxiety for women randomized to the intervention (aOR=0.19, 95% CI: 0.14-0.28). 12% of women in the intervention group developed MDE at six-weeks postpartum, versus 41% in the control group. We found reductions of 81% and 74% in the odds of postnatal MDE (aOR=0.19, 95% CI: 0.13-0.28) and of moderate-to-severe anxiety (aOR=0.26, 95% CI: 0.17-0.40), respectively. The HMHB early prenatal intervention focusing on anxiety symptoms reduced postpartum CMDs. (clinicaltrials.gov#: NCT03880032)

Common mental disorders (CMDs) such as depression and anxiety occur frequently in the perinatal period, often remain untreated and constitute significant global health concerns [1]. Pooled estimates indicate a 29% and 24% self-reported prevalence of elevated prenatal and postnatal anxiety symptoms in the Global South, respectively[2]. The high prevalence of associated symptoms in the prenatal period presents challenges for families and pregnancies, especially in resource-limited settings where mental health services are scarce[3]. Prenatal anxiety predicts anxiety, depression and suicide risk in the postnatal period[4–6]. Anxiety and depression also tend to co-occur[7], with one study from Pakistan reporting that 69% of pregnant women with anxiety disorders also had depression, and 37% of pregnant women with depression also had an anxiety disorder[8]. Additionally, prenatal anxiety is related to poor growth and developmental outcomes in infants[5,9,10]. While the effects of postnatal CMDs are serious, prenatal anxiety is one of the strongest predictors of postnatal CMDs[4,5], is highly prevalent (e.g., affecting between one third and one half of women in Pakistan)[11,12], and is an understudied condition, with the preponderance of epidemiological and intervention studies focused on depression.

Effective treatments exist, but preventive approaches that could reduce the prevalence of severe postnatal depression are lacking[13]. This is critical given the host of negative infant outcomes[14], including impaired physical and cognitive development[15], associated with the condition. Cognitive Behavior Therapy (CBT) is an effective treatment for both anxiety and depression[16,17] and, combined with strategies to address social stressors, has been used effectively for depression in the later prenatal and postnatal period in low-resource settings[18]. However, CBT has rarely been used in primary prevention, an approach that is especially vital in low- and middle-income countries (LMICs) where an enormous treatment gap exists and where those in greatest need often have the least access to mental health care[19–21].

In our formative work (Methods), we sought to understand women's lived experiences of anxiety in the context of Pakistan[22–25]. Using qualitative methods, we documented the social context of the lives of pregnant Pakistani women with at least mild symptoms of anxiety. Salient findings included problems that women face with respect to gender inequalities within their own households, limits on their mobility, and preferences for male children, which are factors that served as sources of anxiety or as obstacles to using available coping mechanisms[24]. Pregnant women's experiences of receiving antenatal care at public medical

facilities were often described in terms of distress, connected to mistrust, and characterized by a lack of respect from some healthcare providers[23]. Though social support was perceived as critical to these women, many described having limited family or peer support, leading them to experience social isolation[25]. Finally, we uncovered pregnancy-specific triggers of anxiety, such as having experienced a prior miscarriage or stillbirth and feeling worried about not giving birth to a boy[22].

The development of interventions involves understanding key sources of anxiety and their impact on the day-to-day lives of the women, as well as trying to address modifiable factors in a culturally acceptable manner using approaches with a sound evidence-base. Therefore, in a phase 3, two-arm, single-blind, randomized controlled trial conducted in Pakistan we aimed to evaluate the effectiveness of this evidence-informed, anxiety-focused early prenatal preventive intervention on the prevalence of postnatal CMDs. We hypothesized that women with subclinical to clinical levels of prenatal anxiety randomized to the intervention arm would have reduced symptoms of anxiety and depression and fewer cases of depression at six weeks during postnatal period relative to the enhanced usual care arm of mothers with similar levels of baseline anxiety who did not receive the intervention.

Results

Patient Disposition

From April 16, 2019 to January 31, 2022, 91,184 women were screened for trial participation. The last follow-up occurred on October 7, 2022. Women were not eligible for the trial if they did not fulfill our inclusion criteria of being at least age 18, residing near the health facility, or being in early to mid-pregnancy. Of the 1,307 remaining women with symptoms of at least mild anxiety, 1,200 (92%) consented to participate, were enrolled in the study, and were randomized to receive either the *Happy Mother-Healthy Baby (HMHB)* intervention or enhanced routine care (Figure 1).

A block-randomized schedule was used to allocate women to the intervention (n=600) and control (n=600) arms. Participants had an average age of 25 (standard deviation (SD) 4.7) years at enrollment, with an average gestational age of 16 (SD=5) weeks. Participants had at least mild anxiety at enrollment by design, with an average Hospital Anxiety and Depression Scale (HADS) anxiety score of 11.0 (SD=2.0). Of 1,200 total participants, 352 (29%) were carrying their first pregnancy, and 499 (42%) had a history of miscarriage or stillbirth prior to enrollment. Participants are described in detail and compared by arm in Table 1.

Women were generally similar at the time of enrollment in the two arms, both in age (average 25.1 and 25.5 for the intervention and control arms respectively, $p = 0.10$) as well as baseline anxiety (HADS score 11.0 in the intervention versus 11.1 in the control arm, $p = 0.53$) and depressive symptoms (HADS score 6.8 in the intervention versus 6.7 in the control arm, $p = 0.51$). Participants in the intervention arm had somewhat lower social support compared to those in the control arm, measured by the Multidimensional Scale of Perceived Social Support (MSPSS) [range 1 to 5][26], with an average score of 3.1 versus 3.3 ($p = 0.04$) related to family support and 3.3 versus 3.5 ($p = 0.05$) related to support from significant others. Participants were similar between arms in their history of stillbirth,

education, family structure, and self-reported monthly income (Table 1). Women were followed through the course of their pregnancies and interviewed again at approximately six weeks after delivery. Of 1,200 women who were randomized, 755 (63%) completed the six-week postnatal interview, which was similar across arms. A comparison of those who completed the six-week postnatal interview and those who did not is shown in Table 2. Women who completed the postnatal interview were similar across arms (Table 3). Loss to follow-up was completely at random with respect to intervention arm (N=380, 63% completed the intervention arm; N=375, 63% completed the control arm), baseline social support, and baseline perceived stress, anxiety, and depression, as determined with Little's missing completely at random test (with ten degrees of freedom, $p = 0.65$).

Primary outcomes

Anxiety and depressive symptoms were measured at the six-week postnatal interview for 755 participants, 380 (50.3%) in the intervention and 375 (49.7%) receiving enhanced-care, who were compared between arms. Using intent-to-treat (ITT) analyses, moderate-to-severe anxiety (based on a symptoms threshold) and diagnosis of depression (based on clinical assessment) were estimated among trial participants and compared between arms separately and as a composite (either/or) using logistic regression, shown in Table 4. We examined the odds ratio representing the effect of the intervention both in the bivariate association based on ITT by arm as well as adjusted for age, income, education, gestational age at enrollment, and first pregnancy. Examined jointly, we found 81% reduced odds of having either a Major Depressive Episode (MDE) or moderate-to-severe anxiety for women randomized to the intervention (aOR=0.19, 95% CI: 0.14-0.28) satisfying the criteria for the primary outcome of the trial. 12% of women in the intervention group developed MDE at six-weeks postpartum, versus 41% in the control group corresponding to a reduction of 81% in the odds of postnatal MDE (aOR=0.19, 95% CI: 0.13-0.28). 9% of women in the intervention group versus 27% in the control group had moderate-to-severe anxiety at six weeks postpartum, corresponding to a 74% reduction (aOR=0.26, 95% CI: 0.17-0.40), respectively.

Secondary outcomes

Although the arms had similar anxiety and depression symptoms at baseline, as noted above, the average postnatal HADS anxiety score among women in the intervention arm was significantly lower than among those in the control arm (3.4 versus 7.2, $p < 0.001$). Depression symptoms (Patient Health Questionnaire (PHQ-9)) were similarly lower among those in the intervention arm compared to those in the control arm (5.5 versus 10.5, $p < 0.001$). Anxiety and depressive symptoms are described in detail by arm in Table 5. The average difference between HADS anxiety score at six-weeks postnatal was estimated with linear regression, and adjusted for age, income, education, gestational age at enrollment, and whether the participant was enrolled during her first pregnancy. This estimated difference (intervention average minus control average) was −3.8 points on the HADS scale (95% CI −4.4 to −3.2, $p < 0.001$). The average difference in PHQ-9 depression score was similarly estimated with linear regression and adjusted for age, income, education, and first pregnancy, with an estimated difference between arms of −5.1 points on the PHQ-9

scale (−5.9 to −4.3, $p < 0.001$). The change over time in anxiety and depression symptoms, measured by the HADS scale, is shown in Figure 2.

Safety

Adverse events and severe adverse events were defined prior to the trial. Women had a total of 58 (4.8%) miscarriages or stillbirths, 27 (2.2%) infant deaths, 3 hospitalizations (0.3%) and 2 suicide attempts (0.2%). The study did not have any unexpected events or adverse events related to the intervention, thus the adverse events that occurred were unrelated to the trial. They were reported to the US National Institute of Mental Health (NIMH) appointed Data Safety and Monitoring Board (DSMB) bi-annually. Sixteen referrals were made based on the type of the event; 14 physical and two mental health related events were referred to Benazir Bhutto Hospital or the Institute of Psychiatry Rawalpindi, Pakistan. None of these events were related to participation in the intervention.

Post-hoc sensitivity analyses

In addition to the analyses reported above, we examined the difference between arms using HADS anxiety at postnatal follow-up while adjusting for baseline HADS anxiety, estimating an adjusted difference of −3.82 (95% CI −4.44 to −3.20), similar to those shown in Table 5. We also examined the differences between arms in the PHQ-9 measured at postnatal follow-up while adjusting for baseline depression, which were similar to the primary analyses (−5.11, 95% CI −5.91 to −4.31).

Discussion

Results of our trial show that an early prenatal intervention to treat symptoms of anxiety had strong preventive effects on postnatal depression in addition to reducing moderate-to-severe symptoms of anxiety. When the combined outcomes of MDE and moderate-to-severe anxiety (including either MDE or moderate-to-severe anxiety as well as both conditions) were examined postnatally, we found a reduced odds of 81% for women who were randomized to the intervention group. Examined separately, we found reductions of 81% and 74% in the odds of depression and of moderate-to-severe anxiety, respectively. This is considered clinically significant[27], corresponding to approximately a five-point decrease in the PHQ-9 for symptoms of depression and to a four-point decrease on the HADS anxiety scale compared to those not receiving the intervention. There were no unexpected events or adverse events related to the intervention observed in the study, indicating that in addition to being effective, the HMHB intervention was also safe for this population.

According to a systematic review, much less attention has been paid to maternal anxiety and stress than depression, and even fewer studies have tested the effects of prenatal interventions on postnatal anxiety[28]. While CBT-based interventions are commonly employed to treat anxiety and depression, or examine interventions targeting perinatal depression (not symptoms of anxiety) only, our approach focused exclusively on women with anxiety symptoms during pregnancy, aiming to prevent the later development of more severe and disabling depressive and anxiety disorders. We also tailored the intervention to

address extended marital family relations and communication, additions beyond CBT-alone that until now have been limited to the parental or spousal relationships[29,30].

A meta-analysis of interventions for prevention of postnatal depression found weak to moderate effects of universal approaches (targeting all women in pregnancy), with CBT being the most commonly employed intervention[31]. Three randomized controlled trials (RCTs) using CBT were reported that focused on women with depression and anxiety and/or stress in pregnancy[16,32,33], but none focused on women with only symptoms of anxiety (without depression) and none of the studies were from LMICs. The intervention content in these studies overlapped with ours in that they all used CBT and a similar number of visits. However, unlike these studies, HMHB was larger, delivered individually, used non-specialist providers (NSPs) to deliver the intervention, and none of our intervention content focused on depression[16,32,33]. Our results indicate that targeting women with symptoms of anxiety early and using potent CBT strategies produces strong effects in preventing postnatal depression.

Regarding studies in South Asia to reduce postnatal depression or anxiety, our prior intervention, the Thinking Healthy Program (THP), was a psychosocial intervention for mothers experiencing perinatal depression that started in the 3rd trimester[18]. THP was also based on CBT, was delivered through female non-specialist providers, and successfully reduced depression in perinatal women by more than half and led to reduced disability and better overall social functioning, with effects sustained at 12 month follow-up[18]. Other studies conducted in Iran, including one trial using a CBT-based intervention focused on at-risk women who were literate, aged 18-32, and in their first pregnancy found that it reduced postnatal depression scores during the third trimester but had no effect on anxiety or self-esteem[34]. Sanaati et al. (2018) and Moshki et al. (2014) employed lifestyle-based education and health locus of control training, respectively[35,36]. Neither study found significant changes in levels of postpartum depressive symptoms, and only the former examined symptoms of anxiety. While efforts to pilot phone- and app-based CBT programs have also been promising[37–39], such trials have been limited in their inclusion criteria and applicability to only women who have independent phone access (e.g. not commonly the case among low-income women in Pakistan) and who live in primarily high-income settings. For example, Guo et al.'s (2020) successful use of a mindful self-compassion intervention to prevent postpartum depression in Tianjin, China, was entirely web-based and limited to women with home internet access[40].

Our study has several implications for future research and practice. Firstly, mild anxiety symptoms in early pregnancy may be a prodrome to later perinatal depression and women should be screened as early as possible. Second, given the scarcity of trained and experienced mental health professionals in LMICs, an effective non-pharmacological intervention for anxiety can be delivered by non-specialists under supervision. Further research can explore the delivery of this intervention through other non-specialists such as prenatal nurses, midwives and community health workers who form the backbone for perinatal health care in most primary and secondary settings. Third, the intervention employs similar active CBT elements and strategies to THP for perinatal depression. In most LMICs, there is likely to be a single delivery-agent for such psychosocial interventions. Future research could therefore focus on combining the two programs into a single transdiagnostic

intervention that could have synergistic effects on both anxiety and depression. Such a transdiagnostic intervention might have in-built assessment procedures that could allow the delivery-agent to personalize the intervention sessions according to individual patient needs. Research should focus on examining the effectiveness and cost-effectiveness of such transdiagnostic and more personalized approaches. The transdiagnostic "common elements' approach could also make training, supervision and practice simpler for non-specialist health workers. More research is also needed to examine other modes of delivery (e.g., group sessions, electronic modalities), the minimum number of sessions needed, as well as the delivery by healthcare workers, such as nurses or community health workers. Future studies are required to understand how HMHB could be adapted to other settings as well as how it might be integrated with other established programs of care for perinatal mental health.

One limitation to our intervention was loss to follow-up. We expected a high attrition rate (30%) among trial participants, however, approximately 37% of women were lost prior to completing final data collection. In addition, 25% of those randomized to the intervention never received any intervention session. Part of the reason for this attrition before women had received any of the HMHB program may be that we did not use strategies to limit post-randomization withdrawals, such as delaying randomization until potential participants returned for the next visit (enabling those who might have consented out of politeness to withdraw passively prior to randomization) rather than randomizing women at the time they were screened.

Regarding loss-to-follow up in later visits, one major impediment appears to have been the COVID-19 pandemic coinciding with our study. Our qualitative research suggested that many women were reluctant to receive care at the hospital during COVID-19 epidemic[41]. NGiven many women are required by their families to be escorted to the hospital, it may have also been difficult for participants to find someone to accompany them (e.g. mothers-in-law often serve in this role, who may also fear COVID-19 because of older age or underlying health issues). Participants may not have felt comfortable leaving friends or neighbors to take care of their children, given the fear of contagion. During a six-month lockdown by the Pakistani government (which was also followed by smaller local lockdowns, some of which affected our catchment population), all in-person study activities were entirely suspended due to COVID-19 restrictions. This meant that women recruited immediately prior to the lockdown had most or almost all of their sessions by phone (including five women who had no in-person sessions). Our qualitative findings suggest that rapport with the therapists was poorer when NSPs were not able to deliver the sessions in person (Atiq et al *submitted manuscript*), likely leading to dropout. However, results also showed that most women preferred a mix of sessions in-person and over the phone, citing advantages to face-to-face sessions (e.g. better comprehension and rapport with the therapist) as well as advantages to phone delivery (e.g. ease of scheduling, no need to leave the home or be accompanied to the hospital) (Atiq et al *submitted manuscript*). Our process evaluation highlighted that some reasons for non-participation included lack of decision-making abilities (needing in-laws' or husband's permission) and sometimes only limited access to other family members' phones for women who could not receive all visits in person[42] (which could have also led to loss to follow up when in-person sessions were not possible). Mental health stigma was also a barrier to participation noted in our evaluation[42].

The possibility of response bias due to social desirability cannot be ruled out although participants were assured their responses would be anonymous and have no bearing on their care. While we did perform statistical analyses controlling for sociodemographic characteristics (in addition to intent-to-treat analyses), there may have been other confounding variables related to the quality of therapist training for which we lacked data. Finally, additional longitudinal follow-up beyond six-weeks postpartum is needed to examine the potential sustained effects of the intervention on participants and its effects on child growth and development of the offspring.

In summary, our study showed that the HMHB intervention for pregnant women with symptoms of anxiety in early- to mid-pregnancy reduced the combined outcomes of MDE and moderate-to-severe anxiety postnatally. This study was carried out in a low-resource setting where specialized mental health care is not readily available. It was also carried out safely with no adverse events resulting from participation in the intervention. Given the mental health treatment gap in LMICs and recommendations for non-pharmaceutical treatment of anxiety during pregnancy generally[43–45], our results on the efficacy of HMHB suggest it should be further tested and adapted for other women with anxiety in low-resource settings. The fact this study was carried out with a ‘talking therapy’ and with non-specialist providers suggests that scale-up may be possible.

Methods

Participants

This study was a phase III, two-arm, single-blind, individual randomized controlled trial (RCT) (Clinicaltrial.gov identifier - NCT03880032). Women were enrolled from the outpatient Obstetrics and Gynecology Department of Holy Family Hospital, a large public tertiary care facility affiliated with Rawalpindi Medical University, in Punjab Province, Pakistan. At the first routine prenatal visit, pregnant women were approached consecutively for recruitment, screening, and consent.

Intervention development process

We recognise that the high rates of common mental disorders in women can be traced to the social circumstances of their lives. Almost three decades ago, Desjarlais et al. (1995) pointed out how ‘hopelessness, exhaustion, anger and fear grow out of hunger, overwork, violence and economic dependence. Understanding the sources of ill health for women means understanding how cultural and economic forces interact to undermine their social status. If the goal of improving women’s well-being from childhood through old age is to be achieved, healthy policies aimed at improving the social status of women are needed along with health policies targeting the entire spectrum of women’s health needs’[46]. The statement is still true today, and we believe interventions such as ours can play a role in highlighting the importance of mental health and empowering women and their families to take positive actions towards its betterment. In fact, our formative research on social and contextual factors to inform the design and implementation of our intervention produced indispensable insights into the lived experiences of Pakistani women in general as well as our target population in particular, namely those who experience anxiety during pregnancy,

and factors facilitating or constraining their engagement with mental health interventions such as ours[22].

Prior to the trial, this qualitative research included interviews with 19 pregnant women fulfilling the inclusion criteria of the trial and 10 healthcare providers in the Department of Gynecology and Obstetrics at the study hospital[22]. Resulting from the analysis of these in-depth interviews was a qualitative study exploring the sociocultural context of prenatal anxiety among Pakistani women from an empowerment perspective through thematic analysis from the formative research phase of this trial. To apply theoretical conceptualizations of gendered power dynamics as a contextual factor in health interventions, we drew on Naila Kabeer's (1999) three-dimensional framework for women's empowerment as presented in her UN Research Institute for Social Development discussion paper[47], which emphasizes the processual nature of women's empowerment and the agency of individual women's choices despite gendered structures of constraint[48–50].

As discussed at length in the findings of our publication, entitled *"A Woman is a Puppet." Women's Disempowerment and Antenatal Anxiety in Pakistan*, we identified major intersections between Pakistani women's perceived sources, mitigators, and coping strategies for prenatal anxiety and their enabling resources, agency, or achievements related to empowerment during pregnancy[24]. Gender inequalities such as unequal control of household finances, limits on women's mobility such as *purdah*, and preferences for male children were described by many respondents as exacerbating anxieties, constraining pregnancy-related decisions, and limiting available coping mechanisms. Avenues of self-advocacy used by many women, including those in patrilocally extended households, consisted primarily of appealing to her husband or returning to her natal home. Although most women described fears of upsetting the *susral* (husband's family), some women reported in-laws being a source of support at home or when accompanying women to doctor appointments. Experiences at medical facilities overall were often depicted in negative terms of distress or distrust, a theme elaborated further in a subsequent paper focused on patient-provider communication in public healthcare settings and the lived experiences of prenatal care and anxiety in Pakistan[23]. Coping mechanisms among participants in formative research interviews included accessing emotional or practical support, seeking positive activities, and engaging in faith-based practices like prayer and reading scripture. Many women, however, particularly those who described having limited family or peer support, endorsed less healthy coping strategies such as self-isolation, fatalism, or physical abuse of children. This finding of isolation was so prominent that we extended our analysis of this theme in another paper entitled, *"Those whom I have to talk to, I can't talk to": perceived social isolation in the context of anxiety symptoms among pregnant women in Pakistan*[25]. Many respondents reported feelings of physical and social isolation, even in the context of joint families with larger social networks. Fearing censure by their in-laws and peers for sharing or seeking help with pregnancy-related anxieties, many women reported relying on husbands or natal family members. Again, normative cultural expectations around pregnancy in Pakistan such as male gender preference, perceived immutability of wives' domestic responsibilities, and expectations of accompanied travel by women were found to be sources of disconnectedness in the prenatal period. Providers whom we interviewed explained social isolation and deficits in social support during pregnancy as key contributors

to worse anxiety symptoms, reduced access to care, and poorer health behaviours. These studies on the lived experiences of our patient population were the outcome of deep and continuous engagement with the community and healthcare workers, and attention to the results of our qualitative analyses were considered essential to intervention design, delivery, and rigorous evaluation[29].

The lived experiences of pregnant women with anxiety were incorporated into the conduct of the clinical trial both based on this extensive formative work that we carried during the first year and a half of the grant prior to the trial[22–25] as well as the process evaluation that was conducted during the trial[29]. In addition to the studies described, to specifically inform intervention development we also used this formative research to explore what pregnant women attributed as the causes of anxiety during different stages of pregnancy, their physical and emotional expressions of anxiety, its impact on daily functioning, their coping strategies to address anxiety, barriers and facilitators to receiving or delivering psychological therapy for anxiety, and how the barriers can be overcome. Based on the findings, the intervention took into account perceived sources of anxiety (e.g. past traumatic experiences of childbirth, lack of trust in health-care services, having insufficient support, and pressure to produce male offspring). The intervention provided information and skills to help negotiate the health system, involved significant family members in care, and gently challenged family attitudes toward male preference. It addressed somatic symptoms through the introduction of relaxation techniques such as breathing exercises and meditation. The intervention educated family members about anxiety and positively reinforced family support. It also recognized and supported alternate sources of coping such as faith and engaging family members to collaborate in care. While we recognize that intimate partner violence (IPV) has a major impact on women's anxiety, addressing IPV within this setting, and through non-specialists, was not found to be viable or feasible. Therefore, we addressed it indirectly by focusing on women's wellbeing, increasing social support from the spouse and other family members, and empowerment. IPV was only touched on directly in the third session that introduced information about different types of IPV and emphasized its harmful effects on women and babies during the perinatal period. The intervention was designed to be easily comprehensible and to use culturally relevant metaphors, idioms, and narratives. Recognising the barriers to accessing mental health care, the intervention was integrated into routine antenatal care and offered flexible appointments and assistance with transport. Finally, it addressed stigma associated with mental health by aiming to educate and empower the women and their families[22].

Non-Specialized Providers (NSPs) and their training, supervision and competency

The Non-Specialized Providers (NSPs) who delivered the intervention were the salaried employees of the host organization in Pakistan. They had completed four years of higher education, including a two-year bachelor's degree and a two-year master's degree in psychology (considered equivalent to a bachelor's degree outside of Pakistan). Crucially however, they were not clinically trained (which requires a minimum of one year of further specialist training) and therefore not licenced to practice as therapists. We classed them as NSPs and were particularly interested in this cadre because psychology is a popular subject for higher education, especially amongst women in Pakistan, but most are unable

to undertake further clinical training due to limited training facilities and supervisors. We wanted to evaluate if this cadre could be competent to deliver an evidence-based therapy after brief training. Female research assistants at the organization who showed interest in receiving the intervention training underwent an extensive 42-50 hours of classroom training conducted by the mental health expert who led the development team of the Happy Mother – Healthy Baby (HMHB) intervention. This training had a strong focus on understanding anxiety and its consequences, acquiring counselling skills, comprehending the key principles of CBT, familiarizing the team with the intervention's content, and mastering the procedures for its delivery.

Research assistants were assessed post-training using the Enhancing Assessment of Common Therapeutic factors (ENACT) scoring system[51]. ENACT has been developed for role play based assessment of mental health and psychosocial support skills for non-specialist and specialist providers. It has 18 items, each domain is assessed using a three-point Likert scale, ranging from "needs improvement" (Level 1) to "done well" (Level 3). These items assess common counselling skills and intervention specific skills. Counselling skills items assess verbal and non-verbal communication, rapport building, self-disclosure, exploration, interpretation, normalization of feelings, empathy, warmth, genuineness, confidentiality promotion, and harm assessment. The intervention-specific items assess knowledge and skill in evaluating problems and their impact on functioning, in providing psychoeducation, facilitating cognitive restructuring and behavioural activation, exploring social support, involving families appropriately, collaborative goal setting, promoting realistic hope, enhancing problem-solving skills, and eliciting feedback during advice, suggestions, and recommendations (see Supplementary Table 1 for a list of ENACT domains).

Research assistants who performed well on ENACT post training were recruited as NSPs for the HMHB trial. They then embarked on field training, which encompassed practical exposure through offering the intervention (six core sessions weekly) to two individuals dealing with perinatal anxiety - under the supervision of a specialist trainer (a PhD level psychologist). A research assistant (referred to as an independent assessor), who had undergone comprehensive HMHB training and received specialized training in conducting assessments, rated two randomly chosen sessions per trainee. Assessments revealing knowledge or skill gaps prompted targeted training in those specific areas requiring attention.

In addition, over the course of the trial, 252 sessions (12% of 2104 sessions) were chosen randomly for assessment using ENACT. The collective evaluation revealed that 91% of the domains in these sessions were rated at Level 3 (done well), 6.9% at Level 2 (done partially), and 0.2% at Level 1 (needs improvement). The results of these evaluations conducted were relayed to the supervisors.

During the trial, the assessments were conducted in a separate room with no interactions between the assessors and intervention team members. Efforts were made to ensure the assessors remained blind to allocation. All participants were given clear instructions not to reveal their allocation status to the assessment team. In case of inadvertent unblinding,

assessment team members were instructed that they should stop the interview and reschedule it with a different assessment team member on another day. Data collected in the assessments were collected via a structured questionnaire on a tablet-based electronic form. The Open Data Kit (ODK) was used to store data in a de-identified format.

Supervision sessions were conducted weekly either face-to-face or online. Most of the sessions were conducted remotely online to mimic real-life situations in most LMIC settings where mental health supervisors are scarce and normally located in urban centers. The supervision was primarily aimed to ensure continuous experiential learning, discuss challenging cases, explore work related stress and to maintain NSPs' motivation. Furthermore, based on the ENACT ratings, constructive feedback was provided to the respective NSP and the opportunity was given to practice skills through conducting role plays during the supervision sessions. These procedures helped ensure the fidelity and quality of intervention delivery.

National lockdown measures in Pakistan, implemented from March to August 2020 due to COVID-19, led to the closure of hospital outpatient departments. Intervention delivery shifted from face-to-face to telephone during this period. Before delivering the telephone sessions, NSPs received five hours of training focusing specifically on essential factors for effectively delivering interventions over the phone. These factors encompassed ensuring participants' privacy and confidentiality (including instructions to verify that participants had a private space in which to speak), implementing strategies to reduce potential distractions, establishing rapport and maintaining participant engagement, incorporating breaks as necessary, and developing contingency plans for situations such as poor connections, dropped calls, or breaches of privacy. Furthermore, the NSPs received instruction on promptly terminating a session upon detection of any indication from the participant of self-harm or harm towards others. They were also trained to conduct a risk assessment in such instances and consult their supervisors (as necessary) if they needed to make appropriate referrals.

The HMHB intervention

While the intervention content was informed by formative qualitative research[22–25], it uses the same core principles and strategies of the Thinking Healthy Program (THP), an evidence-based psychosocial intervention for mothers experiencing perinatal depression[18]. Psychotherapeutic strategies borrowed from the THP included developing empathetic relationships, thought challenging, behavior activation, problem management, and enhancing family involvement and support. These common techniques are also indicated in the transdiagnostic psychotherapy method called the Common Elements Treatment Approach (CETA), developed specifically for use with non-specialist providers in lower- and middle-income countries (LMICs)[52]. We applied these components by guiding women to: 1) identify unhealthy thoughts and behaviors; 2) replace unhealthy thoughts and behaviors with helpful thoughts and behaviors; and 3) practice healthy thinking/behaviors. Customized, culturally relevant illustrations and examples of healthy activities were used in collaboration with the participating women to determine tasks for encouraging engagement in helpful behaviors. HMHB was presented as a 'mother-to-be' program rather than being specifically

targeted for maternal mental health. Involvement of accompanying family members in group sessions was incorporated into three sessions to promote their support. Details of the intervention development process are reported elsewhere[22].

Following the development of the intervention, feedback from participants indicated that the intervention was acceptable, feasible, and helpful[29].

The treatment arm

Women in the treatment arm received six core sessions and were allowed up to 6 supplemental booster sessions of HMHB, a psychosocial intervention based on CBT for expectant women experiencing anxiety during early to mid-pregnancy[22]. The first five core sessions were delivered weekly in early- to mid-pregnancy upon enrollment into the study. The additional booster sessions were offered to all participants and occurred between the fifth session in early- to mid-pregnancy and the final sixth core session in the third trimester. Although each participant could receive a maximum of six booster sessions, no participant got more than four and on average participants received 1.5 (SD=0.78) booster sessions. The booster sessions were coordinated with the routine antenatal appointments (or delivered by phone during the COVID-19 lockdown) and aimed to reinforce HMHB's health messages and to encourage use of problem management strategies to deal with any ongoing or new issues closer to the time of delivery.

Intervention contents were developed for in-person one-on-one sessions and complemented by at-home exercises. Because of the COVID-19 pandemic coinciding with the middle of this trial, 22% of women received at least one session over the phone rather than in person. Participants received facilitated access to medical services (less waiting time) as well as reimbursement for transportation and for any ultrasounds at the hospital needed during antenatal care.

The control arm

Women assigned to the control condition received enhanced routine care alone. This care was 'enhanced' with respect to having facilitated visits with psychiatric care as necessary, transportation reimbursed to and from Holy Family Hospital, calls to remind participants of routine visits, and shorter wait times in the hospital when prenatal visits occurred. Like the intervention group, women in the enhanced routine care arm were also reimbursed for as many ultrasounds as were needed, as determined by their providers.

Inclusion and exclusion criteria

Eligibility was based on the following criteria: mother's age ≥ 18 years, gestational age ≤ 22 weeks, ability to speak Urdu, and intent to reside within 20 kilometers of Holy Family Hospital until delivery. The reason Urdu was used as an inclusion criterion was due to the fact that Urdu is Pakistan's national language and it understood by the majority (over 95%) of people in the study area regardless of their socio-economic background. The inclusion criteria were screening positive for at least mild anxiety and the absence of depression. Screening for at least mild anxiety was based on a score of ≥ 8 on the anxiety subscale of the Hospital Anxiety and Depression Score (HADS)[53], validated in

Urdu[54]. Screening for depression was based on a score of ≥ 8 on the depression subscale of the HADS. Participants who scored ≥8 on both anxiety and depression items were interviewed further to confirm Major Depressive Episode (MDE) with the help of Structured Clinical Interview for DSM IV (SCID). The MDE module was administered by a trained researcher. Other exclusion criteria included serious medical conditions, suicidal ideation, and self-report of past or present major psychiatric disorders (e.g., bipolar affective disorder, schizophrenia) or psychiatric care (e.g., anxiolytic medications, psychotropic drugs or psychological treatment).

Randomization

Participants were randomly assigned to treatment or control study arms before the baseline assessment. Arm assignment was generated using a pseudo random-number generator by a trial statistician in the US based on randomly permuted blocks of size 4, 8, 12 and 16. The assignment list was printed in order, with each step of the sequence stored separately in opaque envelopes and numbered sequentially with a seven-digit code. When an eligible woman provided consent to participate, the next available envelope was pulled and opened, and assignment to intervention or control was recorded. This procedure continued until 600 women in each arm were reached. The randomization allocation was saved in a password protected file in a computer. Only the statistician and the data manager had access to the randomization codes. Outcome assessors were blinded to the trial arm allocation.

Power calculation

To determine statistical power, we assumed a significance level of 0.05 and a conservative outcome prevalence of CMDs (MDE and Generalized Anxiety Disorder - GAD) at 30% (based on the fact that this is lower than most estimates of prenatal depression in Pakistan)[11,12,55,56]. Assuming this prevalence, we calculated needing 840 pregnant women (420 in each arm) to achieve 85% power to detectable a 30% reduction in CMDs (30% in the control arm compared to 21% in the intervention arm). Based on prior studies we considered a 30% reduction in CMDs as a meaningful reduction[1,57–58]. We expected 30% attrition post enrollment; thus we targeted a total enrollment of 1200 women[59].

Study outcomes

The primary outcome of this study was defined as diagnosis of clinical depression or moderate to severe anxiety symptoms (including but not limited to both anxiety and depression). Clinical depression was defined as a diagnosis of a Major Depressive Episode (MDE) by the Structured Clinical Interview for DSM Disorders (SCID) assessed at 6-weeks post-partum. The SCID is a semi-structured interview used to make major Axis I DSM diagnoses. The SCID depressive episode section was translated and culturally adapted using a rigorous procedure developed[60] and used previously in Pakistan[18,60–65]. Our other primary outcomes, also both at six-weeks postpartum, were a diagnosis of MDE alone and moderate to severe levels of anxiety. Moderate to severe anxiety was defined as a threshold of a symptom score >10 using the HADS anxiety subscale[53]. The HADS-Anxiety is a well-established seven-item instrument scored on a four-point Likert scale (range 0–21). The Urdu version has been previously adapted and used in Pakistan[66,67], showing satisfactory reliability and validity[54]. The HADS was selected both because it had been

validated in Pakistan, and in particular because it includes separate subscales for anxiety and for depression. A cutoff of >10 was used as the threshold for moderate to severe levels of anxiety.

In addition to the primary outcomes presented above, secondary mental health outcomes included changes in symptom scores for the depression and anxiety subscales measured on the HADS as continuous outcomes. Depressive symptoms were also measured postpartum using the Patient Heath Questionnaire (PHQ-9), a 9-item instrument (on a 4-point Likert scale; range 0-27) to assess for symptoms in the past 2 weeks[68], which has been previously adapted[69,70] and validated in Pakistan[71,72] and shown high reliability (Cronbach α=0.83)[70].

Other secondary outcomes were specified among neonates born to women participating in the trial. Preterm birth (defined as <37 weeks' gestation), low birthweight (below 2500 grams) and small-for-gestational-age at birth (weight at birth <10th percentile for gestational age) were all defined as secondary outcomes. Due to specific considerations of this population, the analyses for neonates are not presented here.

Exploratory outcomes included conducting analyses to examine mediators of the associations of interest as well as potential moderators of any effects on the intervention on CMDs, depression and anxiety. Specifically, we proposed to study social support and perceived stress as mediators, given the intervention intentionally tried to improve family support by involving family members in some sessions and to reduce stress by teaching relaxation exercises. Another exploratory outcome was cost assessed through a cost-effectiveness analysis using Client Service Receipt Inventory (CSRI) data. The goal of this analysis was to calculate service costs for each participant to compare the costs for the participants in the intervention and control arms (in order to establish the economic savings or expenses between the two groups). Exploratory outcomes will be published separately.

Post-hoc analyses for which there were not hypotheses and were not specified as secondary outcomes but for which we collected data include breastfeeding, intimate partner violence, functional impairment, perceived stress, maternal-child bonding and responsiveness. Post-hoc analyses will be presented in future manuscripts.

Safety and adverse event monitoring

Adverse events were monitored throughout the trial through different mechanisms. Adverse events were reported by the assessment and intervention team who were engaged with the participants as they occurred. After detection, an electronic form was filled out and sent to the data manager via the server. The data manager then generated a report that was sent to an independent physician, who then evaluated whether the event was related or unrelated to the intervention. Depending on the severity of the event, it was then reported to the local IRB and to the NIMH-appointed DSMB. Referrals were made to Benazir Bhutto Hospital and mental health related events were referred to the Institute of Psychiatry Rawalpindi, Pakistan.

Protocol deviations

In the protocol, we planned to diagnose Generalized Anxiety Disorder (GAD) both in combination with MDE as well as on its own as a main outcome. A diagnostic evaluation of GAD was not carried out; thus we lacked this information in our study. We also did not meet our projected sample of 840 women completing the six-week assessment as determined in our sample size calculation. Finally, the COVID-19 pandemic occurred during our data collection, including a lockdown for six months during which we were not able to recruit new participants. All already recruited participants (including women who received few or no sessions in person), were switched to receiving the assessments by phone. Phone sessions were typically shorter than those delivered in person, lasting from 30 to 45 minutes. In spite of the Covid-19 pandemic and a substantial portion of the intervention delivered over the phone, 12% of our sessions were monitored by an independent assessor using ENACT (only slightly short of our goal to monitor 15%). Finally, for logistical reasons, we did not provide additional training to medical staff at the hospital from the depression module of Mental Health Gap Action Program for mental health treatment.

Statistical analyses

We summarized demographic and other baseline characteristics of women enrolled in the trial both overall and by arm, in order to verify that randomization successfully created similar groups of participants. For continuous measurements, we used means and standard deviations as a summary, and for categorical measurements, we used counts and percentages. In order to compare features across arms, we performed standard statistical comparisons such as the Student’s t-test and the Chi-square test, depending on the type of variable. P-values were two-sided. Statistical analyses were performed with R 4.2.0.

MDE as well as symptoms of anxiety using the HADS and depression symptoms using the PHQ-9 at the postnatal visit were examined. These outcomes were compared between arms using linear regression (for symptoms) and logistic regression (for depression diagnosis, the indicator for high anxiety, and the composite measure), both unadjusted as well as adjusted for age, income, education, gestational age at enrollment, and whether the participant was enrolled during her first or later pregnancy. A sensitivity analysis was performed for depression diagnosis and high anxiety symptoms comparing arms while adjusting for baseline depression and anxiety symptoms.

Ethical Approval

Ethical approval for this research was obtained from the Institutional Review Boards of Rawalpindi Medical University, Human Development Research Foundation, and the Johns Hopkins Bloomberg School of Public Health and an NIMH-appointed Data Safety Monitoring Board.

Our methodology was approved by the ethical boards of Rawalpindi Medical University (IRB/RMU-20/12/20190) and the Human Development Research Foundation (IRB# 001-2017) in Pakistan. It was also approved by the Johns Hopkins Bloomberg School of Public Health (IRB# 00009177) and a National Institute of Mental Health (NIMH)-appointed Data Safety Monitoring Board in the US. All participants provided written

informed consent prior to screening and to data collection. The trial was registered at the US National Library of Medicine (clinicaltrials.gov: NCT03880032).

Ethics and inclusion statement

Data were collected in person and by telephone (during the COVID-19 pandemic) by local research staff in a LMIC. Two colleagues, including one of the co-first authors (A. Malik and A. Zaidi) are from Pakistan and reside in the country. Two others, including the senior author (A. Rahman, N. Atif) are from Pakistan and are now based in a high-income country. Three authors are from a high-income country, including the principal investigator and one author who is of Pakistani origin and speaks Urdu (P.J. Surkan, J. Perin, A Rowther). We fully endorse the Nature Portfolio journals' guidance on LMIC authorship and inclusion.

This research is locally relevant to Pakistan and relevant to other countries in the region and the Global South. The authors chose to develop and test an intervention for symptoms of anxiety during pregnancy, since this focus has been largely neglected in the literature both generally and in the region. HMHB also builds upon our prior research in Pakistan, namely THP which also used a CBT approach, but was delivered in late pregnancy/the postpartum period, and from targeted depressive symptoms (rather than prenatal anxiety). Prior to conducting the randomized controlled trial, we engaged in extensive formative research (for over a year) to tailor the intervention to be culturally appropriate and to reflect the needs of our target population[22–25]. This included interviews with women and health care providers to gather their input with the aim of understanding the lived experiences of pregnant Pakistani women with symptoms of anxiety, and how the intervention could best address their needs. We later re-engaged with the population of interest in a qualitative process evaluation to understand what was working well or could be improved[29]. (Please see the section above for details). Thus, this process allowed for the participation of the local target population throughout the process of designing and implementing the intervention.

The data collection and analytic techniques employed raised no risks pertaining to stigmatization, incrimination, discrimination, animal welfare, the environment, health, safety, security or other personal risks. In both the preparatory work for the grant and in the write up of this manuscript we have taken into account local and regional research relevant to our study in the citations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We extend our heartfelt gratitude to the women participants and obstetric staff at the Department of Obstetrics and Gynaecology at Rawalpindi Medical University. Additionally, we are deeply indebted to Prof Muhammad Umar, Prof Rizwana Chaudhri and Prof Asad Tamizuddin Nizami of Rawalpindi Medical University for their unwavering support, both administrative and clinical, spanning the entire trajectory of our research from inception to completion. This study was supported by the National Institute of Mental Health at the US National Institutes of Health Grant # RO1 MH111859 (Received by PI: PJ Surkan). The NIMH had no role in the conduct of this research.

Data Availability Statement

All our data and relevant codebooks have been submitted to the US National Institute of Mental Health's data archive for public access, which can be accessed at https://nda.nih.gov/.

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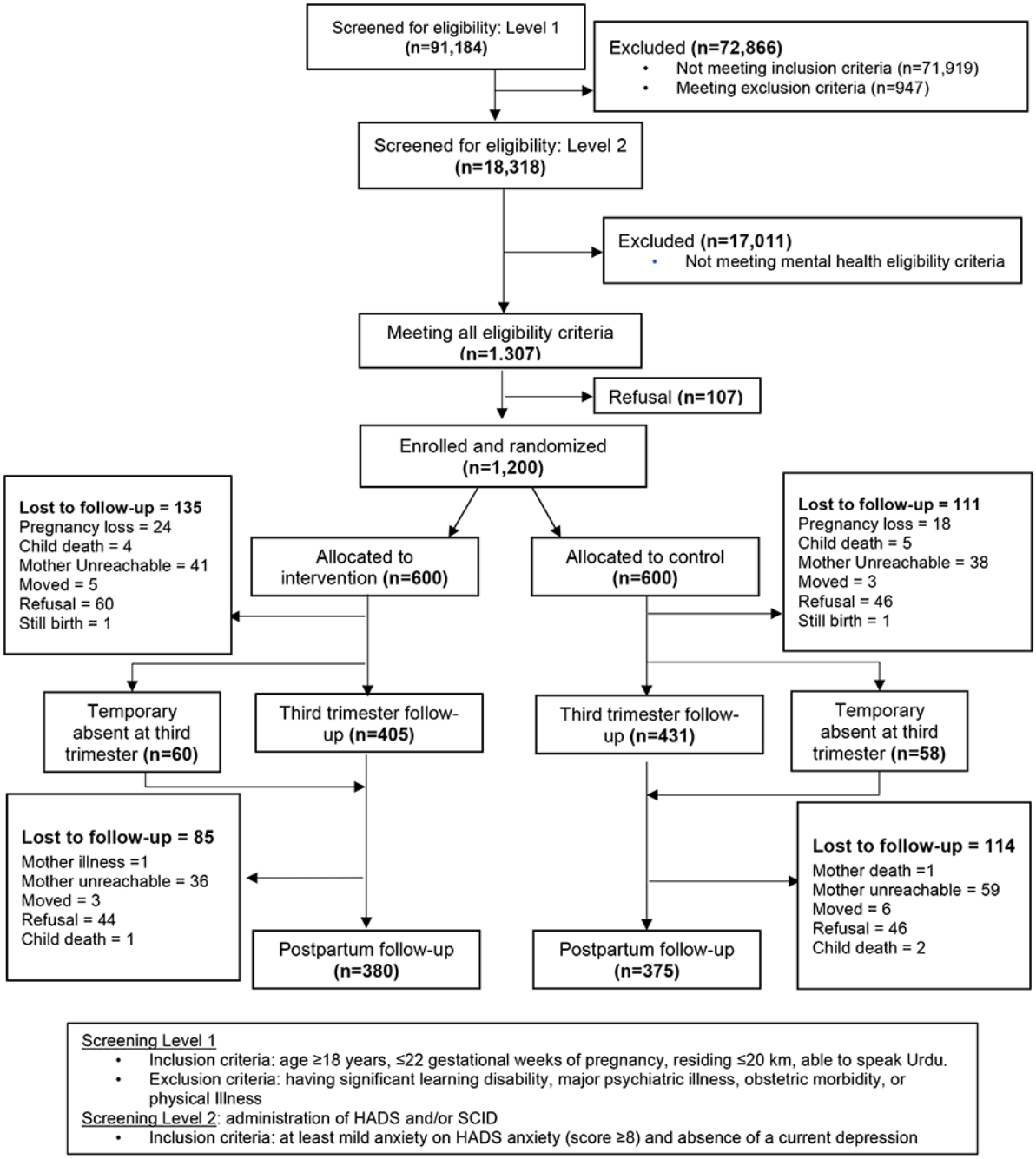

Figure 1:
Consort diagram for the Happy Mother – Healthy Baby (HMHB) randomized controlled trial.

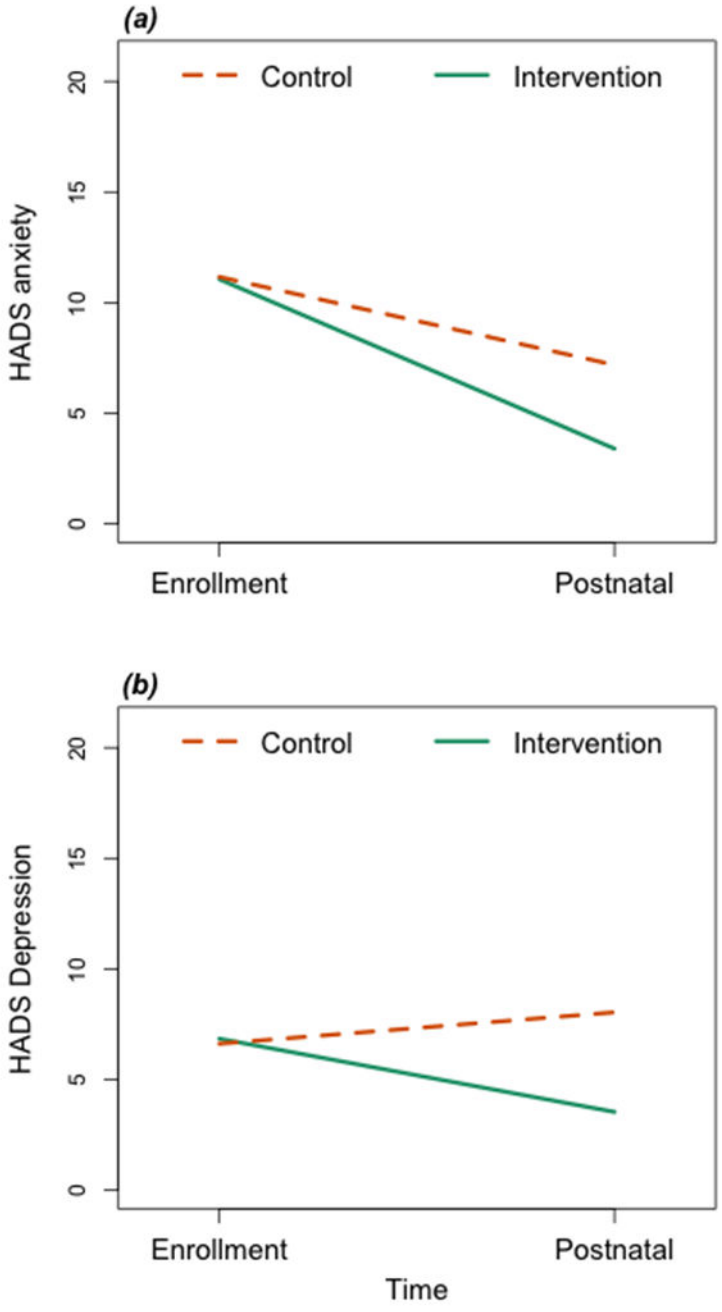

Figure 2.:
Changes in common mental health disorders CMDs, anxiety and depression, due to Happy Mother – Healthy Baby (HMHB). Change in anxiety (a) and depression (b) among 755 women enrolled in the Happy Mother – Healthy Baby (HMHB) trial by arm.

Table 1.

Description of 1200 pregnant women enrolled in the HMHB trial by arm.

	Overall (N=1200)	Intervention Arm (N=600)	Control Arm (N=600)	p*
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	25.3 (4.7)	25.1 (4.6)	25.5 (4.7)	0.096
Gestational Age at enrollment (weeks)	15.5 (4.6)	15.5 (4.6)	15.5 (4.6)	0.737
Anxiety symptoms at enrollment (HADS); range 0 - 21	11.0 (2.0)	11.0 (2.0)	11.1 (2.0)	0.528
Depressive symptoms at enrollment (HADS); range 0 - 21	6.7 (2.8)	6.8 (2.9)	6.7 (2.8)	0.507
Perceived stress at enrollment (PSS-10); range 0 - 40	20.1 (2.9)	20.2 (2.8)	20.1 (2.9)	0.449
Social support (MSPSS)				
Significant other; range 1 – 5	3.3 (0.9)	3.3 (0.9)	3.4 (0.9)	0.048
Family; range 1 – 5	3.2 (1.0)	3.1 (1.0)	3.3 (0.9)	0.035
Friends; range 1 – 5	3.2 (1.0)	3.1 (1.0)	3.2 (0.9)	0.059
	N (%)	N (%)	N (%)	
Maternal age ≤25 years	562 (47%)	290 (48%)	272 (45%)	0.325
Married	1200 (100%)	600 (100%)	600 (100%)	1.000
First pregnancy	352 (29%)	167 (28%)	185 (31%)	0.281
Residing with at least one child	673 (56%)	337 (56%)	336 (56%)	1.000
History of stillbirth or miscarriage	499 (42%)	257 (43%)	242 (40%)	0.412
Education level				0.766
≤ Primary school	333 (28%)	172 (29%)	161 (27%)	
Middle school – matriculation	551 (46%)	273 (46%)	278 (46%)	
≥ Intermediate	316 (26%)	155 (26%)	161 (27%)	
Family structure				0.799
Nuclear	376 (31%)	191 (32%)	185 (31%)	
Joint (parents)	413 (34%)	201 (34%)	212 (35%)	
Extended (parents and siblings)	411 (34%)	208 (35%)	203 (34%)	
Monthly income (PKR)				0.992
Low (<20,000)	568 (49%)	285 (49%)	283 (49%)	
Middle (20,000-35,000)	443 (38%)	220 (38%)	223 (38%)	
High (>35,000)	154 (13%)	77 (13%)	77 (13%)	

*Significance by two-sided Student's t test for continuous factors, Chi-square test for categorical factors.

HADS – Hospital anxiety and depression scale; MSPSS – Multidimensional scale of perceived social support; MRQ – Marital relationship quality.

Table 2.

Description of 1200 pregnant women enrolled in the HMHB trial comparing those who completed trial to those who were lost to follow-up.

	Completed trial (N=755)	Did not complete trial (N=445)	p*
	Mean (SD)	Mean (SD)	
Age (years)	25.3 (4.6)	25.3 (4.7)	0.964
Gestational Age (weeks)	15.8 (4.5)	15.1 (4.6)	0.009
Anxiety at enrollment (HADS)	11.1 (2.0)	11.0 (2.0)	0.627
Depression at enrollment (HADS)	6.7 (2.8)	6.9 (2.9)	0.250
Perceived stress at enrollment (PSS-10)	20.1 (2.9)	20.2 (2.8)	0.362
Social support (MSPSS)			
Significant other	3.3 (0.9)	3.3 (0.9)	0.979
Family	3.2 (0.9)	3.2 (1.0)	0.917
Friends	3.2 (0.9)	3.2 (1.0)	0.935
	N (%)	N (%)	
Randomized to receive the HMHB intervention (Yes)	380 (50%)	220 (49%)	0.811
Maternal age ≤25	351 (46%)	211 (47%)	0.802
Married	755 (100%)	445 (100%)	1.000
First pregnancy (Yes)	210 (28%)	142 (32%)	0.150
Residing with at least one child	436 (58%)	237 (53%)	0.146
History of stillbirth or miscarriage (Yes)	328 (43%)	171 (38%)	0.100
Education level			0.020
≤ Primary school	190 (25%)	143 (32%)	
Middle school – matriculation	352 (47%)	199 (45%)	
≥ Intermediate	213 (28%)	103 (23%)	
Family structure			0.539
Nuclear	245 (32%)	131 (29%)	
Joint (parents)	254 (34%)	159 (36%)	
Extended (parents and siblings)	256 (34%)	155 (35%)	
Monthly income (PKR)			0.009
Low (<20,000)	336 (45%)	194 (44%)	
Middle (20,000-35,000)	300 (40%)	151 (34%)	
High (>35,000)	119 (16%)	100 (22%)	

*Significance by Student's t test for continuous factors, Chi-square test for categorical factors.

HADS – Hospital anxiety and depression scale; SD – standard deviation

Table 3.

Baseline Description of 755 pregnant women who completed the HMHB trial by arm.

	Overall (N=755)	Intervention Arm (N=380)	Control Arm (N=375)	p*
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	25.3 (4.6)	25.2 (4.7)	25.4 (4.6)	0.418
Gestational Age at enrollment (weeks)	15.8 (4.5)	15.7 (4.5)	15.8 (4.5)	0.792
Anxiety symptoms at enrollment (HADS)	11.1 (2.0)	11.0 (2.1)	11.1 (1.9)	0.709
Depressive symptoms at enrollment (HADS)	6.7 (2.8)	6.8 (2.9)	6.6 (2.6)	0.380
Perceived stress at enrollment (PSS-10)	20.1 (2.9)	20.2 (2.9)	20.0 (2.9)	0.268
Social support (MSPSS)				
Significant other	3.3 (0.9)	3.3 (0.9)	3.4 (0.8)	0.184
Family	3.2 (0.9)	3.1 (1.0)	3.3 (0.9)	0.086
Friends	3.2 (0.9)	3.2 (1.0)	3.2 (0.9)	0.255
	N (%)	N (%)	N (%)	
Maternal age ≤25 years	351 (46%)	179 (47%)	172 (46%)	0.789
Married	755 (100%)	380 (100%)	375 (100%)	1.000
First pregnancy	210 (28%)	99 (26%)	111 (30%)	0.314
Residing with at least one child	436 (58%)	217 (57%)	219 (58%)	0.775
History of stillbirth or miscarriage	328 (43%)	172 (45%)	156 (42%)	0.346
Education level				0.450
≤ Primary school	190 (25%)	101 (27%)	89 (24%)	
Middle school – matriculation	352 (47%)	174 (46%)	178 (47%)	
≥ Intermediate	213 (28%)	105 (28%)	108 (29%)	
Family structure				0.831
Nuclear	245 (32%)	126 (33%)	119 (32%)	
Joint (parents)	254 (34%)	124 (33%)	130 (35%)	
Extended (parents and siblings)	256 (34%)	130 (34%)	126 (34%)	
Monthly income (PKR)				0.530
Low (<20,000)	336 (45%)	167 (44%)	169 (45%)	
Middle (20,000-35,000)	300 (40%)	149 (39%)	151 (40%)	
High (>35,000)	119 (16%)	64 (17%)	55 (15%)	

*Significance by two-sided Student's t test for continuous factors, Chi-square test for categorical factors.

HADS – Hospital anxiety and depression scale; MSPSS – Multidimensional scale of perceived social support; MRQ – Marital relationship quality.

Table 4.

Effects on mental health conditions among 755 women who completed the HMHB trial.

	Anxiety†	Depression‡	CMD (Anxiety, Depression or both)
Intervention Arm (N=380); N(%)	33 (8.7%)	44 (11.6%)	57 (15.0%)
Control Arm (N=375); N(%)	100 (26.7%)	152 (40.5%)	178 (47.5%)
Odds Ratio (reference Control) (95% CI)	0.26 (0.171, 0.400)	0.19 (0.132, 0.280)	0.20 (0.138, 0.276)
p*	7.0 ×10^E-11	2.8 ×10^E-20	1.7 ×10^E-22
Adjusted Odds Ratio**	0.26 (0.167, 0.393)	0.19 (0.129, 0.275)	0.19 (0.132, 0.268)
p**	4.7 ×10^E-10	5.5 ×10^E-18	1.6 ×10^E-20

† Defined as a HADS anxiety score of >10.

‡ Defined as a Major Depressive Episode by the Structured Clinical Interview for DSM Disorders (SCID).

* Difference and significance determined by logistic regression, significance shown as two-sided.

** Estimated with logistic regression, adjusted for age, income, education, first or later pregnancy, and gestational age at enrollment.

Table 5.

Effects on mental health symptoms at six weeks postnatal, among 755 women who completed the HMHB trial.

	Anxiety Symptoms (HADS, range 0-21)	Depressive Symptoms (PHQ-9, range 0 - 27)
Intervention arm (N = 380); Average (SD)	3.40 (3.96)	5.45 (5.46)
Control arm (N = 375); Average (SD)	7.19 (4.69)	10.52 (5.75)
Difference (reference control): Estimate (95% CI)	−3.78 (−4.403, −3.165)	−5.08 (−5.875, −4.275)
p *	2.8 ×10^E-30	2.1 ×10^E-32
Adjusted Difference (reference control): Estimate (95% CI) **	−3.80 (−4.414, −3.181)	−5.09 (−5.880, −4.282)
p **	9.3×10^E-31	1.6 ×10^E-32

* Difference and significance determined by linear regression, significance shown as two-sided.

** Estimated with linear regression, adjusted for age, income, education, first or later pregnancy, and gestational age at enrollment.