Impact of prenatal maternal depression on gestational length: post hoc analysis of a randomized clinical trial

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Summary

Background Shortened gestation is a leading cause of childhood morbidity and mortality with lifelong consequences for health. There is a need for public health initiatives on increasing gestational age at birth. Prenatal maternal depression is a pervasive health problem robustly linked via correlational and epidemiological studies to shortened gestational length. This proof-of-concept study tests the impact of reducing prenatal maternal depression on gestational length with analysis of a randomized clinical trial (RCT).

Methods Participants included 226 pregnant individuals enrolled into an RCT and assigned to receive either interpersonal psychotherapy (IPT) or enhanced usual care (EUC). Recruitment began in July 2017 and participants were enrolled August 10, 2017 to September, 8 2021. Depression diagnosis (Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; DSM 5) and symptoms (Edinburgh Postnatal Depression Scale and Symptom Checklist) were evaluated at baseline and longitudinally throughout gestation to characterize depression trajectories. Gestational dating was collected based on current guidelines via medical records. The primary outcome was gestational age at birth measured dichotomously (≥39 gestational weeks) and the secondary outcome was gestational age at birth measured continuously. Posthoc analyses were performed to test the effect of reducing prenatal maternal depression on gestational length. This trial is registered with ClinicalTrials.gov (NCT03011801).

Findings Steeper decreases in depression trajectories across gestation predicted later gestational age at birth, specifically an increase in the number of full-term babies born ≥39 gestational weeks (EPDS linear slopes: OR = 1.54, 95% CI 1.10–2.16; and SCL-20 linear slopes: OR = 1.67, 95% CI 1.16–2.42). Causal mediation analyses supported the hypothesis that participants assigned to IPT experienced greater reductions in depression symptom trajectories, which in turn, contributed to longer gestation. Supporting mediation, the natural indirect effect (NIE) showed that reduced depression trajectories resulting from intervention were associated with birth ≥39 gestational weeks (EPDS, OR = 1.65, 95% CI 1.02–2.66; SCL-20, OR = 1.85, 95% CI 1.16–2.97).

Interpretation We used a RCT design and found that reducing maternal depression across pregnancy was associated with lengthened gestation.

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Keywords: Prenatal; Birth outcome; Depression; Randomized clinical trial (RCT); Gestational age at birth (GAB)

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Research in context

Evidence before this study

As highlighted by the World Health Organization and the March of Dimes, shortened gestation is one of the leading causes of child morbidity and mortality with lifelong health consequences for both physical and mental health. Despite the magnitude of this problem, there is a lack of progress in reducing rates of early delivery. Shortened gestation is a multifaceted public health problem that will require varied approaches to address. Prenatal depression reduction is one viable approach. Maternal depression is associated with shorter gestation based on robust metanalytic evidence. We searched PubMed, from database inception to March 8th, 2024, for papers published in English, using the search string: (depress*) AND (pregnan* or antepartum OR prepartum OR antenatal OR prenatal OR perinatal) AND (labor OR birth OR childbirth OR obstetric OR delivery) AND ("gestational age" OR "gestation* length"). Our search yielded 696 results. We have recently shown that a brief, safe and cost-effective prenatal psychosocial intervention (brief interpersonal psychotherapy, IPT) profoundly decreases depression during pregnancy. Thus, this post hoc analysis of a randomized clinical trial (RCT) provides an opportunity to test the benefit of depression reduction on gestational length.

Added value of this study

Presented here is a first-of-its-kind, proof-of-concept study showing that improving prenatal maternal mental health by reducing depression in a RCT extends gestational length. We show that 1) decreasing depression trajectories over pregnancy leads to increased gestational length and 2) mothers in the depression treatment group have a steeper decline in depression over pregnancy and this decline mediates the association between depression treatment and gestational length. Notably, the effect of reducing depression over pregnancy for increasing gestational length was observed in a racially and ethnically diverse population of 226 mother-infant dyads with relatively low household income.

Implications of all the available evidence

The present study demonstrates that providing effective mental health support to pregnant individuals that reduces depression, is a plausible approach to lengthening gestation. Study findings support the possibility that implementation of efficacious psychosocial interventions can yield benefits not only for the mother, but for offspring as well. Babies born full term and after 39 gestational weeks are significantly less likely to require Neonatal Intensive Care Unit (NICU) stays and to experience cognitive and behavioral challenges later in life. Thus, shifting the distribution of deliveries to increase those at later gestational ages, will yield both cost saving and long-term public health benefits.

Introduction

Shortened gestation is the leading cause of death for children under five years and profoundly affects health, including substantially elevated neonatal morbidities.[1–6] The enhanced risk to babies for these morbidities as well as adverse long-term outcomes extends across the full gradient of gestational ages at birth.[5,7–11] For example, respiratory distress and Neonatal Intensive Care Unit (NICU) admissions are 3 times higher for infants born in the 37th week compared to those born after 39 gestational weeks.[6,12] Additionally, children born earlier, including those born in the late preterm and early term period (35–38 gestational weeks) relative to later term deliveries (39–41 gestational weeks) are more likely to show developmental effects (e.g., lower cognitive and educational attainment) over their lifespan.[8,10,13–15] Despite the known public health consequences of shortened gestation and the availability of medical interventions, obstetricians and gynecologists and other international health panel experts have noted the extreme challenge in making progress on extending gestational length. Simply put, shortened gestation has remained an intractable, and multifaceted public health problem that continues to exert tremendous personal, familial, and societal costs.[1,2,4–6] Considerable public health impact can be achieved with scalable, noninvasive efforts that increase gestational length. The primary goal of this study is reporting on one approach that could "move the needle" through this first-of-its-kind, proof-of-concept for improving maternal mental health to extend gestational length and increase the number of babies born full term and after 39 gestational weeks.

Shortened gestation is triggered by multiple, interacting biological and environmental factors, including history of preterm birth, multiple gestations, chronic health conditions, stress, and certain uterine and/or cervical problems. Many processes, across multiple levels of analyses (e.g., genetic, biological, physiological, psychological, systematic, and structural), are known to affect the timing of birth.[16–21] According to prior meta-analytic correlational and epidemiological research, prenatal maternal depression represents one robust risk factor for shortened gestation.[22–24] Evidence from these correlational studies suggests that interventions to reduce maternal depression during pregnancy could improve birth outcome by decreasing the risk for early delivery.

To evaluate the possibility that depression reduction could lead to longer gestation, certain key gaps in the methods and designs of previous studies need to be addressed. The evidence to date establishing prenatal maternal depression as a risk factor has relied primarily

on observational studies showing associations between depression and shorter gestational length.[22,25] The extant literature, based on epidemiological and correlational designs can evaluate associations between depression and earlier birth, but does not test the potential impact of an intervention that manipulates or changes depression trajectories (i.e., decreasing) across pregnancy on timing of birth.[26–28] Here, we implement a longitudinal randomized clinical trial (RCT) design to reduce depression trajectories among pregnant individuals.[27,29] We then test whether decreasing the trajectory of depression over gestation increases gestational length, therefore increasing the number of babies born after 39 gestational weeks.

Results of our previously published RCT demonstrated that a brief, noninvasive, psychosocial intervention (brief interpersonal psychotherapy [IPT]) leads to a steeper decline in depression trajectories, measured repeatedly across pregnancy, compared to enhanced usual care (EUC).[29] Among pregnant individuals assigned to IPT, on average there was a 50% decline in self-reported symptoms and a 5-fold decrease in clinical depression diagnosis (from 37% at baseline to 6% by end of gestation for clinical diagnosis of depression, i.e., major depressive disorder, MDD). Among the individuals assigned to EUC (standard of care supplemented with psychoeducation, referrals, and follow-up), depression also declined over pregnancy (between 13% and 33% for self-report measures of symptoms and from 37% at baseline to 26% by end of gestation for clinical diagnosis of MDD). Thus, results of this RCT demonstrate that while depression trajectories declined for both the IPT and EUC groups, the magnitude of the decline (effect size) was significantly larger for the IPT group relative to EUC.

The current study uses this longitudinal prenatal depression data from individuals participating in this RCT to investigate whether decreasing prenatal depression could increase gestational length in a socioeconomically, racially, and ethnically diverse population. We hypothesized that: 1) in the overall sample, a steeper rate of decline in depression over pregnancy would predict increases in the number of infants born at or after 39 gestational weeks as well as increases in gestational length measured continuously and 2) because individuals randomized to IPT exhibit steeper decreases in depression compared to those randomized to EUC, this greater reduction in depression symptoms among those randomized to IPT would lead to (mediate) later delivery (more infants born after 39 gestational weeks). We identified 39 weeks as the cut off based on The American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine's updated guidelines advocating for full term delivery at ≥39 gestational weeks whenever possible.[30] The RCT design with repeated assessments of prenatal depression symptoms provides a strong examination of the benefit of depression reduction on lengthening gestation. In sum, evidence from this study can provide proof of concept for how to effect improvement on the complex, multifaceted public health problem of preterm birth.

Methods

Study design

We conducted a randomized clinical trial and recruited 234 pregnant individuals primarily from obstetrics clinics at two major medical centers in the Denver, Colorado metropolitan area. Posthoc analyses determined the effect of reducing maternal depression during pregnancy on gestational length. This trial is registered with ClinicalTrials.gov (NCT03011801).

Participants

Recruitment began in July 2017 and participants were enrolled August 10, 2017, to September, 8 2021. Eligibility criteria included 18–45 years of age, English-speaking, 25 weeks gestational age (GA) or less, singleton pregnancy, and endorsing elevated depression symptoms when screened as part of standard of care (Edinburgh Postnatal Depression Scale score ≥ 10).[31] Exclusion criteria included current illicit drug or methadone use and major health conditions requiring invasive treatments (e.g., dialysis, blood transfusions, chemotherapy). Additional assessment for eligibility was performed at baseline to exclude: 1) current or past psychosis or mania, and 2) currently receiving cognitive behavioral therapy or IPT. The analytic sample was 226 due to 1) miscarriage, pregnancy loss, or stillbirth (n = 4), 2) twin pregnancy (n = 1) and 3) loss to follow up (n = 3) (See Consort Diagram, Fig. 1).

Randomization and masking

Eligible participants were assessed at baseline for depression, including both diagnostic and dimensional assessments described below and then randomly assigned to IPT or Enhanced Usual Care (EUC) using a computer-generated random numbers sequence. Participants were randomized with a one-to-one ratio of IPT to EUC, in blocks of two and stratified on current MDD, GA (above or below 15 weeks), and Medicaid status for each study arm. Participants were randomized into IPT or EUC by study therapists. Research staff masked to condition performed interviews for depression assessment, medical record reviews and collected sociodemographic and obstetric data.

Procedures

Participants completed study measures via REDCap and with blinded evaluator at the following timepoints: 1) baseline M = 16.7 gestational weeks (prior to intervention), 2) M = 22.2 weeks, 3) M = 25.8 weeks, 4) M = 29.7

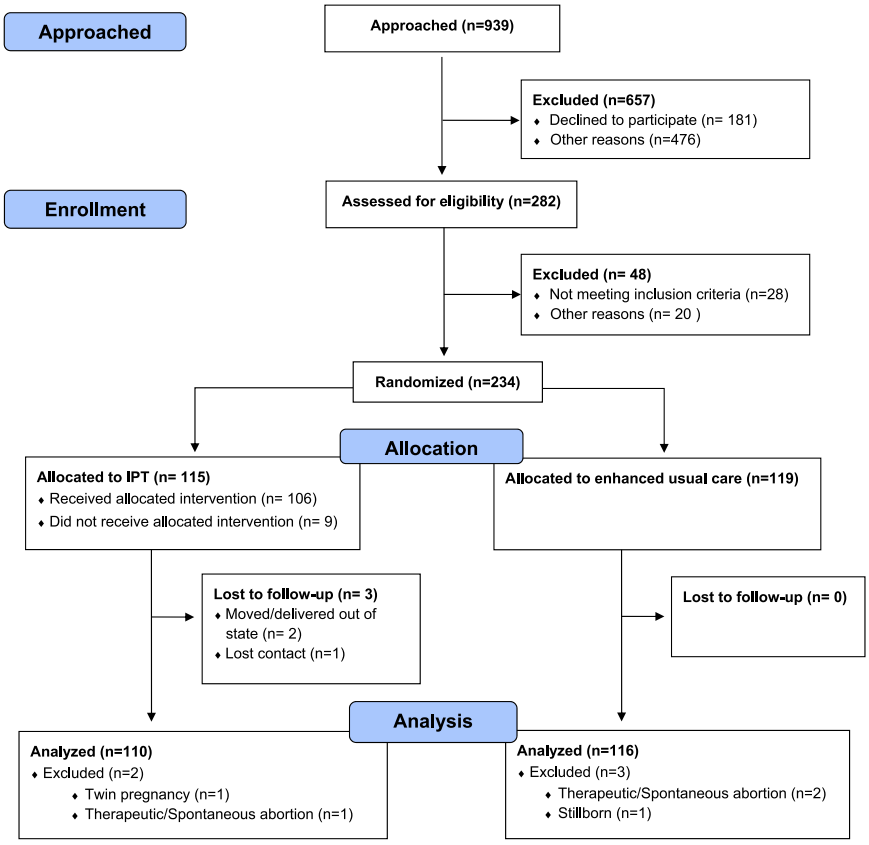

Fig. 1: Consort diagram.

weeks (near end of active IPT), and 5) M = 35.8 weeks (end of gestation).

Intervention conditions

Our prenatal depression intervention, MomCare, and its efficacy are detailed in Hankin et al., 2023. MomCare is a form of brief IPT that is culturally relevant and applies a collaborative care model.[32] MomCare consists of 8 weekly, 50-min individual sessions. Most participants attended nearly all 8 prenatal IPT sessions (M = 7.18 [3.54]). The enhanced usual care (EUC) group received standard of care through their provider that was then augmented in several ways, including a 1-h psychoeducation session with a clinician, ongoing monitoring throughout the prenatal period, and Maternity Social Services (MSS) which provides mental health counseling integrated within the obstetric setting. In the analytic sample, individuals in the MomCare condition showed robust decreases in depression including a 5-fold decrease in MDD status from 36.4% to 6.4% and a 47.7% (SCL20) to 52.2% (EPDS) decrease in symptoms.[29] In the trial pregnant individuals in the EUC condition showed a decrease in MDD status from 36.2% to 25.0% and 13.6% (SCL20) to 32.7% (EPDS) decrease in symptoms. Participants assigned to IPT showed significantly greater MDD remittance and depression symptom reduction relative to EUC.

Measures

Edinburgh Postnatal Depression Scale (EPDS), a 10-item measure employing a 0–3 Likert scale was administered at 5 intervals across gestation (baseline, 22-, 26-, 30-, and 36-gestational weeks) to assess depression symptoms. The EPDS has robust reliability and validity during pregnancy.[33] Total scores range from 0 to 30 with scores ≥10 suggesting probable depression.[31] Internal consistencies were above 0.80 across all five timepoints.

Symptom Checklist (SCL-20), comprises 20 depression items from the Symptom Checklist-90-R item scale and was administered three times during gestation (baseline, 30- and 36-gestational weeks). Responses are recorded on a 0–4 Likert scale and summed to generate a total score, ranging 0–80. Prior research validates use of this measure during pregnancy. Higher scores indicate greater depression and scores below 20 indicate MDD remission.[34,35] Internal consistencies were above 0.90 across all three timepoints.

Structured Clinical Interview for *Diagnostic and Statistical Manual* of Mental Disorders, Fifth Edition; DSM 5 (SCID-5). At baseline and before randomization the SCID-5 was administered by independent evaluators to screen for exclusion criteria of mania or psychosis (current or lifetime) and to determine MDD diagnostic status using *DSM 5* criteria. Additionally, independent evaluators blinded to condition determined MDD status at the end of pregnancy including the two weeks prior to delivery via postpartum interviews. Interviewers were highly reliable: review of 50% of randomly selected SCID-5 yielded kappas ≥ 0.95 for MDD.

Birth outcomes

Two research staff blinded to participants' treatment condition performed medical record reviews to obtain gestational dating. Gestational age was calculated from medical records review applying American College of Obstetricians and Gynecologists guidelines of first trimester ultrasound and/or date of the last menstrual period.[36] The primary outcome was dichotomized as term delivery after 39 weeks' (≥39 weeks' gestational age at birth) and early delivery (<39 weeks' gestational age at birth). The secondary outcome was gestational age at birth measured continuously. Additional obstetric information including parity and presence of labor during delivery (spontaneous labor vs. induced/cesarean-section without labor) were obtained from medical records.

Demographic characteristics

Research staff blinded to condition also collected sociodemographic characteristics based on self-report including birthdate, household income, number of individuals in the household, cohabitation with partner, marital status, educational attainment, and race and ethnicity. Income-to-needs ratio (INR) was calculated by dividing the total reported household income for the past year by the federal poverty threshold for that year corresponding to the number of persons living in the household, specified by the United States Census Bureau.[37]

Statistical analysis

Analyses were conducted with an intent to treat approach. We hypothesized that more rapidly decreasing trajectories of depression symptoms (assessed via SCL-20 and EPDS) throughout pregnancy would 1) relate to longer gestation and 2) mediate the intervention effect on gestational length such that participants assigned to IPT experienced greater reductions in depression trajectory symptoms. We tested our hypothesis via causal mediation analyses, as implemented via the marginal mediation model[38] and including covariates in the model. Causal mediation analyses offer advantages over traditional mediation models (e.g., [39]) that assume there are no extraneous variable (i.e., unmeasured confounders) that influences both the mediator and the outcome, referred to as sequential ignorability.[40] Because measures of a mediating process are typically not randomized, which would protect against unmeasured confounding, we tested our hypothesis using causal mediation analyses, which relaxes the sequential ignorability assumption, as implemented via the marginal mediation model.[38–40] See Supplement for additional discussion of the causal mediation framework. Primary analyses assessed gestational age at birth dichotomously (≥39 gestational weeks vs. <39 gestational weeks) to test clinically relevant cut offs. Because gestational age at birth is continuous in nature, secondary analyses used gestational age at birth assessed continuously. The marginal mediation model produces the significance of the multiplicative paths from 1) intervention (IPT vs. EUC) to the outcome of gestational length (path c), 2) intervention to more rapid depression symptoms trajectory as the mediator (path a), and 3) steeper reductions in depression relating to increased gestational length as outcome (path b). This analytic approach controls for intervention to produce a test of the mediator (indirect effect), called the natural indirect effect (NIE). Path c' corresponds to the direct effect in mediation, called the controlled direct effect (CDE), which relates intervention effects on gestational length as outcome after including depression trajectories as the mediator. Modern approaches testing mediation do not require the individual paths in the model to be statistically significant.[41,42] Mediation is determined in the causal mediation modeling approach by evaluating the NIE.

We tested exploratory hypotheses via moderated mediation. These exploratory analyses evaluated whether maternal MDD diagnosis at baseline, psychotropic medication use, gestational age at randomization, income to needs ratio, presence of labor, and infant sex at birth moderated the expected primary mediation effect. We selected moderators for inclusion in exploratory analyses to test clinically relevant factors that may impact efficacy of the intervention on the outcome including depression severity at baseline (MDD status), use of psychotropic medication, and gestational weeks at randomization. We further included sex at birth based on evidence of sex-specific responses to the intrauterine environment and INR based on known links to fetal development and birth outcomes.[19,43–47] Finally, we included presence of labor (spontaneous labor vs. induced/cesarean section without labor) as potentially linked to our outcome of gestational age at birth. Extending the causal mediation model and including covariates, we added potential moderators one-at-a-time to produce interactive terms that were each analyzed separately.

All models were fit using SAS 9.4. As done with our earlier RCT report, hierarchical linear modeling (HLM)[48] showed that depression symptom trajectories

(SCL-20 and EPDS) were modeled best via linear change over pregnancy, with time defined as weeks after randomization (see Supplement for details). Effect sizes for the primary dichotomous outcome (≥39 weeks' gestational age at birth for later full term delivery; and early delivery <39 weeks' gestational age at birth) of gestation length are provided via odds ratio (*OR*) for the effect of linear depression trajectories across pregnancy onto full-term (or early) birth outcome. Effect sizes for secondary outcome of continuous gestational age at birth are estimated as Cohen's *d*.[49]

Statistical power (see Supplement for details) was estimated to be 82% (for EPDS trajectories) and 78% (for SCL-20 trajectories) to significantly (alpha = 0.05, two-tailed test) predict gestational age at birth (with partial eta effect sizes = 0.19 for EPDS and 0.18 for SCL-20). For the causal mediating analyses, we estimated 81% power to detect significant partial mediation with sample size (n = 226), assuming small effects for treatment on the mediator (depression trajectories, ρ = 0.2) and small-medium effects for the indirect effect (proportion of treatment effect = 0.67), respectively.

Ethics statement

The University of Colorado Anschutz Medical Campus and the University of Denver Institutional Review Boards for the Protection of Human Subjects approved study protocols. Participants provided written and informed consent.

Role of the funding source

The funding source, the National Institute of Health (NIH), did not play any role in study design, in the collection, analysis and interpretation of data, in writing of the report, or in the decision to submit the paper for publication.

Results

Fig. 1 provides the consort diagram and illustrates allocation to intervention condition and participant flow. Within the analytic sample (110 IPT; 116 EUC), 101 received intervention and 9 participated in no intervention sessions. All 226 participants (including the 9 receiving no intervention) were considered part of the study once randomized (intent-to-treat design [ITT]). Participants reported their race and ethnicity as follows: 19.0% Latine; 42.9% non-Hispanic/Latine white, 8.8% Black, 4.4% Asian, 0.4% Native Hawaiian/Pacific Islander, and 24.3% Multiracial and/or Multiethnic. Participants ranged in age from 18 to 42 years (M = 29.75, SD = 5.80) at recruitment. Median annual household income was $50,000 (equivalent median for Denver is $72,661 per 2020 census,[50] and 41.1% of participants were living at or near federal classification of poverty (less than 200% household income-to-needs ratio). Table 1 provides sample baseline characteristics delineated by group.

Preliminary analyses

Retention rates through prenatal assessments were 89% in IPT and 90% in EUC ($\chi^2(1)$ = 0.02.; p = 0.89). Approximately half of the participants (55.3%) delivered after 39 weeks (primary outcome). Visual inspection of the continuous gestational age at birth (secondary outcome) showed slightly skewed distribution. Applying Box–Cox power transformations to gestational age at birth showed that the logarithm of gestational age at birth normalized the distributions, which was used as outcome for secondary analyses. All observed data were used to create a complete data set via Markov Chain Monte Carlo (MCMC) imputation methods[51]; this complete data set was used for analyses. Refer to Supplement for more details on the MCMC process. The RCT design stratified on gestational age at recruitment, Medicaid status and MDD diagnosis, and as expected these variables did not differ between groups. Only parity differed between intervention groups, so it was included as covariate; no other baseline variables were significantly different between groups.

Decreasing depression symptom trajectories predict longer gestation

Individuals with more rapidly declining linear depression trajectories across pregnancy (steeper slope) were significantly more likely to deliver at a later gestational age, defined as birth at ≥39 gestational weeks (EPDS linear slopes: $X^2(1)$ = 6.27, p = 0.01, OR = 1.54, 95% CI 1.10–2.16; and SCL-20 linear slopes: $X^2(1)$ = 7.59, p = 0.006, OR = 1.67, 95% CI 1.16–2.42). The odds of achieving term delivery at 39 weeks' gestational age at birth or later increased by 54.3%, and 67.4%, respectively, with every standard deviation decrease in depression trajectory, as measured by the EPDS and SCL-20. Similarly, the secondary outcome of continuous gestational age at birth was significantly associated with decreases in depression trajectories (EPDS: z = 2.63, p = 0.0009, d = 0.35, 95% CI 0.09–0.61; SCL-20: z = 2.02, p = 0.043, d = 0.28, 95% CI 0.02–0.54).

Causal mediation analyses

With support for the first hypothesis that decreasing trajectories of depression symptoms across pregnancy predicted longer gestation, we proceeded to test the next hypothesis that participants assigned to IPT would experience greater reductions in depression symptom trajectories, which in turn, would contribute to extended time for gestation prior to delivery. Results from causal mediation analyses supported this hypothesis.

For EPDS, path a was significant (intervention effect on depression trajectory; z = 3.33, p = 0.0009, d = 0.49, 95% CI 0.22–0.75, see Fig. 2A) as was path b for the critical test of the natural indirect effect (NIE) showing

Sample characteristics at recruitment	No. (%)	
	IPT Group	EUC Group
No.	110 (48.7%)	116 (51.3%)
Maternal age at recruitment, mean (SD)	29.5 (5.9)	30.0 (5.8)
Gestational age at recruitment, mean (SD), week	18.3 (4.4)	18.0 (4.5)
Parity (nulliparous)	57 (51.8%)	46 (39.7%)
Race and ethnicity		
Asian	6 (5.5%)	4 (3.4%)
Black	10 (9.1%)	10 (8.6%)
Hispanic or Latine	19 (17.3%)	24 (20.7%)
Native Hawaiian/Pacific Islander	1 (0.9%)	0 (0.0%)
Non-Latine White	46 (41.8%)	51 (44.0%)
Multiracial/Multiethnic	28 (25.5%)	27 (23.3%)
Annual household income, median (IQR), $	47,000 (24,500, 88,500)	50,000 (25,600, 95,000)
Household income to needs ratio (living below 200% of the federal poverty line)	43 (39.4%)	49 (42.6%)
Medicaid status (enrolled)	54 (49.1%)	61 (52.6%)
Cohabitating with partner	82 (74.5%)	86 (74.1%)
Education (highest degree earned)		
<High school	6 (5.5%)	6 (5.2%)
High school	23 (20.9%)	21 (18.1%)
Some college	31 (28.1%)	36 (31.0%)
College degree	32 (29.1%)	36 (31.0%)
Graduate degree	18 (16.4%)	17 (14.7%)
MDD diagnosis at recruitment	40 (36.4%)	42 (36.2%)
Psychotropic medication use	20 (18.2%)	29 (25.0%)
EPDS at recruitment, mean (SD)	11.71 (4.83)	11.90 (4.99)
SCL-20 at recruitment, mean (SD)	27.64 (13.88)	27.66 (14.43)
Sample characteristics at the end of gestation	**No. (%)**	
	IPT group	EUC group
Neonate sex (female)	56 (50.9%)	62 (53.4%)
Presence of spontaneous labor (vs. induced or cesarean section)	54 (49.5%)	55 (47.4%)
Gestational age at birth, mean (SD), week	38.8 (1.7)	38.7 (1.8)

EUC, enhanced usual care; IPT, interpersonal psychotherapy; MDD, major depressive disorder; EPDS, Edinburgh Postnatal Depression Scale; SLC-20, Symptom Checklist-20.

Table 1: **Baseline characteristics.**

that reduced depression trajectories were associated with birth ≥ 39 gestational weeks after controlling for treatment group (z = 2.05, p = 0.04, d = 0.35, OR = 1.65, 95% CI 1.02–2.66). Likewise, for SCL-20, path a (z = 5.19, p < 0.0001, d = 0.71, 95% CI 0.44–0.98, see Fig. 2B) and path b for NIE (z = 2.50, p = 0.012, d = 0.38, OR = 1.85, 95% CI 1.16–2.97) were both significant. Effect sizes for these results indicate that the odds of full term birth at ≥39 weeks increased, on average, by 65.0% and 85.3% for each standard deviation decrease in depression trajectory (EPDS and SCL-20, respectively) across pregnancy. Fig. 3A & B depicts results for the mediational model.

Similar support was obtained for gestational age at birth as a continuous outcome in these mediation analyses. For EPDS trajectories, both path a (z = 3.33, p = 0.0009, d = 0.49, 95% CI 0.22–0.75) and path b for the NIE (z = 2.07, p = 0.039, d = 0.28, 95% CI 0.02–0.54) were significant. For trajectories of SCL-20, path a (z = 5.19, p < 0.0001, d = 0.71, 95% CI 0.44–0.98) was significant, and path b for the NIE (z = 1.88, p = 0.06, d = 0.25, 95% CI –0.01 to 0.51) had a p value of 0.06. Fig. 3C & D depicts these mediation results.

Moderated mediation analyses

Mediational analyses find that allocation to IPT more effectively reduces depression trajectories across pregnancy relative to EUC, and in turn, depression reduction predicts full term birth at ≥39 weeks. Thus, exploratory analyses examined whether demographic or clinical factors moderated these indirect effects. Results yielded no significant effect (p's > 0.54) of moderated mediation, including for maternal MDD diagnosis at the beginning of the trial (z = 0.60, p = 0.55 for EPDS, OR = 1.16, 95% CI 0.72–1.87; z = 0.31, p = 0.76 for SCL-20, OR = 1.08, 95% CI 0.67–1.74), gestational age at randomization (z = 0.47, p = 0.64 for EPDS, OR = 1.12, 95% CI 0.70–1.81, z = –0.28, p = 0.78 for SCL-20,

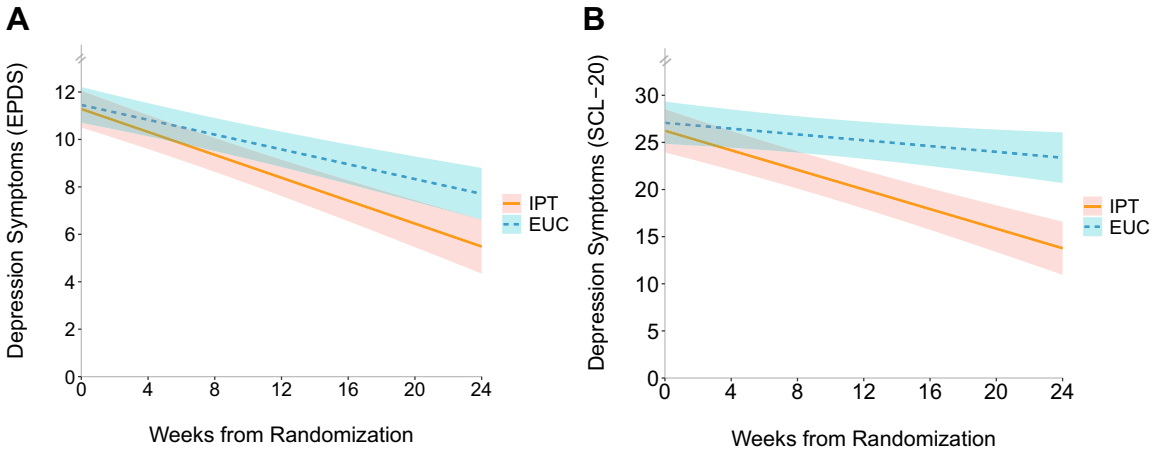

Fig. 2: Effect of intervention (IPT vs. EUC) on prenatal depression symptom (EPDS and SCL-20) trajectories. Note: the color shaded regions represent 95% confidence bounds. Intent to Treat analyses (IPT n = 110; EUC n = 116) showed significant intervention X time interaction with differential improvement for IPT relative to EUC on EPDS (z = 3.33, p = 0.0009, d = 0.49, 95% CI 0.22–0.75) and SCL-20 (z = 5.19, p < 0.0001, d = 0.71, 95% CI 0.44–0.98) depression symptoms over time. The hash mark at the top of the Y-axis indicates the EPDS and SCL-20 ranges go to 30 and 80 respectively.

OR = 0.93, 95% CI 0.58–1.51), psychotropic medication use (z = 0.18, p = 0.86 for EPDS, OR = 1.04, 95% CI 0.64–1.68, z = –0.03, p = 0.98 for SCL-20, OR = 0.99, 95% CI 0.62–1.60), INR (z = 0.19, p = 0.85 for EPDS, OR = 1.05, 95% CI 0.65–1.69; z = 0.24, p = 0.81 for SCL-20, OR = 1.06, 95% CI 0.66–1.71), presence of labor (z = –0.54, p = 0.59 for EPDS, OR = 0.87, 95% CI 0.54–1.41, z = –0.21, p = 0.84 for SCL-20, OR = 0.95, 95% CI 0.58–1.53), and infant biological sex (z = 0.10, p = 0.92 for EPDS, OR = 1.03, 95% CI 0.63–1.65; z = 0.38, p = 0.70 for SCL-20, OR = 1.10, 95% CI 0.68–1.77). See Supplement for additional details.

Discussion

The high prevalence of early birth has remained relatively stable.[52,53] Experts have called for progress on this public health problem given the high prevalence, alongside elevated morbidity and other negative lifespan outcomes associated with shortened gestation, even among babies born in the early term period at less than 39 weeks'.[6,8,10,13–15] Correlational and epidemiological research consistently link maternal depression with earlier gestation. Building on these findings, results from the current study indicate that reducing maternal depression across pregnancy via a cost-effective, noninvasive intervention program (brief IPT) lengthened gestation, increasing the number of infants born full term and after 39 gestational weeks. This effect was observed in a racially and ethnically diverse population with a relatively low-household income to needs ratio. Further, results were maintained across income level, baseline depression severity, and gestational age at randomization. Taken together, these findings provide important proof of concept, namely that treatment of depression was effective among pregnant individuals and support the argument that reduction of depression may be one path towards decreasing the risk of shortened gestation.

There are many factors controlling gestational length. The problem of early birth is complex with known and unknown contributors. Reducing prenatal maternal depression is one pathway that may shift the distribution of deliveries towards later full term (after 39 weeks'). Twenty-six percent of all deliveries occur in the early term period (37–38 weeks')[54] thus, shifting the distribution of gestational ages would result in meaningful increases in the numbers of infants born after 39 gestational weeks. The present findings reveal that decreasing depression symptoms across pregnancy leads to between 65% and 85% increased odds in likelihood of delivery at ≥39 gestational weeks for each standard deviation decrease in depression trajectory. There are profound benefits of delivery at 39 gestational weeks or later on neonatal and lifespan health.[8,10,13–15] Our findings support the conclusion that reducing depression trajectories across pregnancy both promotes maternal mental health and improves birth outcome.

Depression is known to be a leading cause of disease burden that disproportionately impacts women, especially those from socioeconomically disadvantaged contexts.[55–58] Rates of depression are high during gestation and may contribute to disparities in birth outcomes.[59,60] Brief-IPT is one efficacious method of reducing maternal depression during pregnancy.[32,61] Our clinical trial demonstrates pronounced decreases in both clinical depression diagnosis (MDD) and depression symptoms resulting from brief-IPT in a racially and

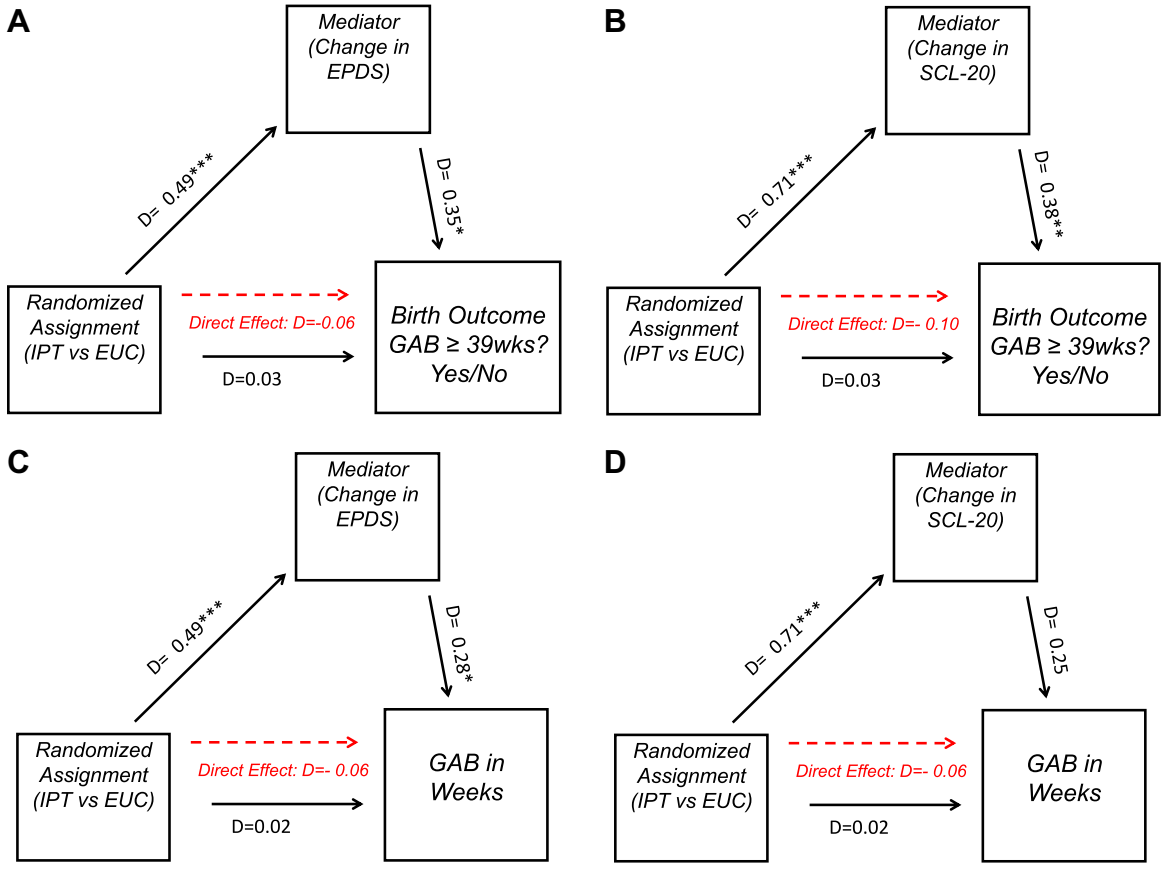

Fig. 3: Causal mediation models: reducing prenatal depression mediates the effect of IPT on gestational age at birth. **A and B** illustrates the direct effect of the intervention and the change in depression on term birth (≥ 39 gestational weeks). The indirect path reveals that reducing depression (EPDS, A) and (SCL-20, B) via brief-IPT mediates the association between intervention and increased likelihood of later term birth (≥ 39 gestational weeks). **C and D** illustrates the direct effect of the intervention and the change depression measured continuously. The indirect path shows that reducing depression (EPDS, C) and (SCL-20, D) via IPT mediates the association between intervention and GAB. Note: Cohen's d is presented for effect size: d > 0 indicates greater depression reduction for IPT compared to EUC for the a path; more depression reduction associated with longer gestation for the b path; and longer gestation for IPT relative to EUC for the c and c' path. The c path is the total effect (solid line), and c' path indicates the direct effect (dotted line). Statistical significance of the effects size are indicated as follows *p < 0.05, **p < 0.01, ***p < 0.001.

ethnically diverse population.[29] Although participants in the EUC group additionally showed decreases in depression, the magnitude of the effect was significantly smaller for the EUC relative to the IPT group. Given the observed benefit of diminishing depression during gestation on birth outcomes, study findings, serve as proof-of-concept that efficacious prenatal mental health interventions represent a viable approach to addressing the problem of early delivery. Further, given concern regarding impacts of psychotropic medication on fetal development,[62] psychosocial interventions provide an efficacious alternative treatment option to relieve prenatal maternal depression symptoms. As such, relatively low-cost psychosocial interventions, such as brief-IPT, may exert great benefits for both maternal and offspring health and well-being.[27,63–66]

This study has a number of important strengths. First, by implementing posthoc analyses of a RCT to reduce prenatal depression we can apply a more direct test of the benefit of reducing prenatal depression on promoting longer gestation. Specifically, by changing depression trajectories over gestation (decreasing) with a manipulation (brief-IPT) we can increase confidence that the declining depression trajectories are a pathway leading to increased gestational length. Second, pregnant individuals were enrolled because they experienced clinically meaningful elevations in depression symptoms based on screening implemented as part of standard obstetric care. By leveraging standard of care screening, this study represents a feasible model for identifying individuals who may benefit from support. Third, mothers and their offspring were followed

prospectively, and depression was assessed three to five times throughout gestation to evaluate links between changes (slope) in depression symptoms over pregnancy and gestational length. Fourth, the causal mediation statistical approach, as opposed to traditional approaches to mediation (e.g., [39]), accounts for potential unmeasured confounds, which is possible when the mediator is measured after randomization.[38] Finally, we include a population that is racially, ethnically, and socioeconomically diverse. Forty percent of participants in this study were living at or near poverty as designated by federal criteria and the median household income was about $30,000 below the median for the Denver metropolitan area. The benefits of depression reduction were observed independent of socioeconomic factors that often challenge dissemination of efficacious interventions supporting generalizability of study findings.

Study findings need be evaluated within the context of several limitations. First, we showed that diminishing depression trajectories during pregnancy can lengthen gestation. There are a multitude of reasons and processes for early birth. Our study focused on depression reduction as one pathway to address the persistent problem of early birth. We directly acknowledge that treating depression does not address the structural, societal, current and historical problems that contribute to disparities in depression and early delivery.[59] Rather, we suggest that providing support to pregnant individuals is one pathway that may improve neonatal and lifespan outcomes for offspring. Second, we note that although we applied best practices for gestational dating using American College of Obstetricians and Gynecologists guidelines,[36] gestational dating is imprecise. However, our RCT design involves randomization of individuals to intervention such that treatment groups did not differ in gestational age at randomization. Third, rates of preterm birth consistent with national norms in the United States, thus there were relatively few (10.2%) preterm deliveries before 37 weeks' gestation in this sample, and thus were not able to test reduction of births prior to this cut off. Last, the intervention was administered in English in the context of a metropolitan area within the United States. Future work should further address the generalizability of study findings given that depression and preterm birth impact disease burden worldwide. Finally, our study was powered to detect effect sizes of r = 0.2 or larger and it is plausible that small but clinically meaningful effects in moderated mediation analyses were not detected. Additionally, power analyses for causal mediation are still in development and thus, a priori calculations were built on traditional mediational models (i.e.,[67]) which could be over or underestimating power.[68]

The mechanisms by which prenatal depression reduction may benefit gestational length are unknown. There are a number of plausible pathways by which reducing prenatal depression may benefit gestational length.[69,70] First, reducing depression may lead to behavioral changes including improved sleep,[71–73] physical activity[74] and diet[75,76] that impact prenatal maternal health and gestational length. Second, reducing depression may improve social relationships, interpersonal communication, and self-advocacy skills which may improve outcomes via improved interactions with the healthcare system and utilization of available healthcare services as well as increased social support.[77] Finally, depression reduction may alter physiological processes, including stress physiology, such as the production of placental corticotropin releasing hormone that regulates the timing of parturition, sleep, and inflammatory mechanisms that impact preterm birth.[16,73,78–82]

Shortened gestation is a currently intractable problem with broad public health consequences and contributes to racial, ethnic, and socioeconomic disparities in health. The present findings provide proof-of-concept evidence that intervening to reduce prenatal depression is an effective, feasible, safe, and low-cost option with benefits for birth outcomes. Integration of depression reduction programs into collaborative care models that combine mental health support with obstetric care may provide a pathway towards improving birth outcomes with long term benefits for population health.

Contributors

Conception, design (EPD, NG and BLH), acquisition (EPD, CHD, NG and BLH), literature review, analysis, and interpretation (EPD, CD, LD, RJG and BLH), accessed and verified the data (EPD, CD, RJG and BLH) drafted and revised the work (EPD, CHD, LD, RJG, MCH and BLH).

Data sharing statement

Deidentified data along with data dictionary are deposited in NDA in compliance with NIMH requirements and upon reasonable request. Study documents such as protocols are available upon request.

Declaration of interests

EPD, CHD, LD, MCH and BLH have no conflict of interest to declare. RJG and NG received payment as consultants via NIH grant R01 MH109662 to the University of Denver.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102601.

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