Beyond Progesterone and Estrogen: Maternal Psychiatric Disturbances Linked to Adrenal Androgens

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Abstract

Perinatal psychiatric disturbances are significant medical conditions that can have tragic sequelae, yet their genesis remains undetermined. While a causative role for estradiol and progesterone has been hypothesized, empirical support is inconclusive. This study was designed to measure steroid hormone concentrations during and after pregnancy and to determine which, if any, were associated with development of significant perinatal mental illness.

Methods: Twenty-eight, healthy primigravid women aged 21-40 yrs consented to participate in this study. Salivary samples for progesterone (P), estrone (E1), estradiol (E2), estriol (E3), testosterone (T) and dehydroxyepiandrosterone sulfate (DHEAS) were collected at 37 weeks of pregnancy and within the first 10 days postpartum and quantified by enzyme-linked immunosorbent assay. Concurrently, nine psychiatric dimensions were assessed using the Symptom Checklist 90R.

Results: No negative mood symptoms were associated with P, E1 or E3 either pre- or postpartum. Negative mood symptoms were associated with T and DHEAS in the full perinatal period, but with E2 post-delivery only.

Conclusion: These findings suggest that adrenal androgen synthesis marked by diminished late pregnancy testosterone and elevated puerperal DHEAS may underlie perinatal mental illness. While further investigation is merited, measurement of testosterone and DHEAS in late stage pregnancy may prove useful as predictors of postpartum psychiatric complications.

Introduction

The psychiatric sequelae from many endocrine disorders have been clearly elucidated. By comparison, the endocrine changes associated with pregnancy and postpartum are some of the most profound in nature, and yet, puerperal psychiatric disturbances are more often attributed to psychosocial stressors or the exacerbation of pre-existing conditions than to specific endocrine factors. While the stress of childbirth and childrearing cannot be discounted and changes in reproductive hormones may well trigger the relapse of pre-existing conditions, it is biologically plausible that such large disruptions in internal chemistry, as occur during pregnancy and following parturition, would also elicit psychiatric disturbances. This becomes especially evident when one considers the dramatic and well-documented influence that steroid hormones have on central nervous system (CNS) activity (1).

Progesterone and its metabolites are potent positive allosteric modulators of the y-aminobutyric acid (A) type ($GABA_A$) chloride channels producing dose-dependent effects ranging from sedation to anesthesia (2). Similar to the benzodiazepines, progesterone is a powerful sedative, hypnotic, anxiolytic and anticonvulsant when administered acutely (2). However, as with benzodiazepines, chronic administration of progesterone produces both psychological and physiological tolerance and withdrawal symptoms marked by an increase in anxiety type symptoms (3,4) similar to those commonly articulated by postpartum women.

Estradiol's excitatory role in hippocampal synaptogenesis and rodent learning is well documented (5). In addition, estradiol modulates the release of dopamine (DA) in the nigrostriatal and mesolimbic pathways via multiple mechanisms and increases serotonin (5-HT) and cholinergic activity throughout the CNS (5). Consistent with the positive effects on monoamine levels and cholinergic activity, estradiol replacement has been shown to alleviate psychiatric distress in some, though not all, postpartum women (6,7) and to improve cognitive performance and psychological well-being in postmenopausal women (8). Unfortunately, only tenuous connections between changes in progesterone, progesterone metabolites, estradiol and/or estriol and varying degrees of postpartum depression have been established (9,10,11,12,13,14,15,16,17), suggesting the possibility

that either other hormones and/or other symptoms are involved in postpartum psychiatric illness.

That other hormones might be involved in puerperal psychiatric distress is not difficult to hypothesize. The changes to maternal chemistry during pregnancy and again following parturition are vast and systemic and the inter-individual variation in hormone metabolism is tremendous. From approximately eight weeks of pregnancy onward, steroidogenesis becomes a complex, multi-compartment process with input from maternal, fetal and placental endocrine glands. The traditionally investigated reproductive hormones, previously synthesized primarily in maternal ovarian tissue, now derive largely from fetal and placental sources (18). The fetal adrenals produce large quantities of dehydroepiandrosterone sulfate (DHEAS) from which estriol, but also testosterone and estradiol are metabolized (19). DHEAS like progesterone and estradiol, is neuroactive with diverse interactions throughout the CNS (20). It is a particularly potent $GABA_A$ antagonist (21). Against the backdrop of plummeting postpartum progesterone and estradiol, changes in maternal DHEAS concentrations likely influence both the concentrations of its downstream derivatives such as testosterone and the estrogens, but also may impact psychological well-being. Preliminary reports in non-pregnant populations support this hypothesis, with both abnormally low and high DHEAS altering testosterone and estradiol concentrations and negatively impacting mental health (22,23,24,25,26,27).

Thus, in recognition of the enormous changes in puerperal hormones and their potential contribution to a variety of psychiatric symptoms (28), the present study prospectively assessed the relationships between six steroid hormones (progesterone, DHEAS testosterone, estrone, estradiol and estriol) and nine psychiatric symptom clusters using the Symptom Checklist 90-Revised (SCL-90-R) (29) in a cohort of healthy primigravid women. To identify premorbid hormonal and symptom patterns and to minimize physiological and psychological adaptation following parturition, hormone values and psychiatric symptoms were measured in late pregnancy and again in the early postpartum period. The goals of this pilot study were to prospectively investigate the incidence and breadth of symptoms relative to puerperal hormones and to determine if the puerperal hormone concentrations of women who developed psychological disturbances were significantly different from those who remained asymptomatic. It was hypothesized that the potential diminishment of GABAergic activity in late pregnancy and especially following parturition, would elicit a broader array of anxiety type symptoms than is typically measured under the current baby blues and postpartum depression syndromes. A secondary goal of this study was to examine the potential associations among hormones and psychiatric symptoms in order to inform future research investigations in this area.

Methods

Volunteer Recruitment: Healthy, primigravid women, aged 21-40 years, were recruited from area childbirth education classes over the course of 10 months in 2004-2005. Participants were excluded from the study if there was a history or current evidence of: illicit drug or alcohol use/abuse, use of psychotropic or other medications that might confound hormone or psychiatric variables and/or prior or concurrent psychiatric, neurological or endocrine system illness. A total of 75 women expressed interest in the study. Thirty-five were disqualified for health or medication issues. Thirty-eight women enrolled in the study. Six gave birth before 37 weeks of pregnancy, 32 entered the study and 28 completed the study. Of the four participants who failed to complete the study, three were lost to attrition and one participant expressed significant postpartum distress and felt unable to continue. This study was approved by the University of Nevada, Las Vegas Institutional Review Board. All women voluntarily provided written, informed consent prior to enrollment.

Study Procedures: All assessments were conducted in the participants' home or place of employment (pregnancy only). Testing was conducted at 37 weeks of pregnancy +/-2 days (T1) and again within 10 days after delivery (T2). At each session, the SCL-90-R (29) was administered to determine the presence and severity of psychological distress and salivary specimen were collected for measurement of steroid hormones. The SCL-90-R is a 90-item self-report inventory designed to measure the severity and intensity of psychiatric symptoms in both inpatient and outpatient populations (29). Participants rated the severity of distress experienced during the prior seven-day period using a 0-4 Likert-type scale (0=no distress-"not at all" to 4=extreme). Symptoms measured included: anxiety, hostility (aggression, irritability, etc.) phobic anxiety, paranoid ideation, psychoticism, somatization (perceptions of pain or other physical disturbances), obsessive-compulsive behavior, interpersonal sensitivity (feelings of personal inadequacy), depression and the global severity index (GSI), which reflects the overall symptom severity. Psychometric data suggests high

construct validity between the SCL-90-R subscales and other measures of psychiatric assessment (29).

Steroid Hormone Analysis: Non-stimulated saliva specimens were collected for the quantification of progesterone, DHEAS, testosterone, estrone, estradiol and estriol. The morning of each test session, before eating drinking or brushing their teeth, participants' saliva was collected by expectoration over a 30-minute period between 8:30 and 9:00 AM. For the postpartum testing session, participants were further instructed to avoid breastfeeding within two hours of the collection interval to prevent feeding-stimulated hormone release that might confound results. Specimen were shipped by two-day courier to the analytical facility (AllVia Diagnostic Laboratory, Phoenix, AZ) where they were stored at -20 C° for <24 hours, then thawed and analyzed for progesterone, DHEAS, estrone, estradiol and estriol concentrations by enzyme-linked immunosorbent assays (ELISA). Testosterone was measured using luminescence immunoassay (LIA). The lower and upper bounds of quantification were as follows: Progesterone 10-3000 pg/mL; DHEAS 100-12,000 pg/mL; testosterone .3-760pg/mL; estrone .3 pg/mL-60 pg/mL; estradiol .1-100 pg/mL; estriol 1-4000 pg/mL. Intra- and inter-day coefficients of variation for each analyte did not exceed 10%, except for inter-day estrone which was 16.25%.

Statistical Analysis: Raw SCL-90-R scores for each symptom cluster were calculated and converted to standardized T-scores using data and methods established by the test authors (29). The T-scores were then compared to previously established, normative standards for non-patient women (34).

Bivariate Pearson product-moment correlations were calculated to assess the relatedness of steroid hormone concentrations and SCL-90-R scores. Normality was tested using the Shapiro-Wilks' W statistic. SCL-90-R symptom scales and progesterone, estrone, estradiol and estriol concentrations were normally distributed. DHEAS and testosterone data were not distributed normally and were, therefore, transformed using a square-root transformation as indicated by the Box-Cox transformation procedure. Correlations between the transformed values of DHEAS and testosterone and SCL-90-R scales did not differ in magnitude or in significance from those using non-transformed values and, therefore, non-transformed values are presented here.

We present correlative data for psychiatric symptoms and a broad array of hormones both during pregnancy and postpartum. It should be noted that the correlations presented in this pilot study are meant to provide a basis for future investigation, and therefore should not be construed as definitive associations. The large number of correlations calculated and the relatively small sample size in this pilot study precluded the use of Bonferonni adjustments to the p-values reported for the tests.

Based upon the observed patterns of correlations, additional analyses were conducted. Participant data were collapsed into two groups, symptomatic and asymptomatic, based upon the presence/absence/severity of pregnancy or postpartum symptoms. Symptomatic was defined as having an SCL-90-R T-score >60 (equivalent to 1 SD above the mean and an 84th percentile ranking) in four or more symptom clusters. Group hormone concentrations were then analyzed using Fisher's exact test to examine proportional equivalence among those women with psychiatric symptoms and their hormone concentrations. The statistical software package SPSS 13.0 (SPSS Inc., Chicago, IL) was used for all data analyses.

Results

Demographics and Pregnancy Outcome: Thirty-two participants were tested at T1 (37 weeks +/- 2 days) and 28 were re-tested at T2 (<10 days postpartum). The T1 hormone sample for one participant was lost by the courier. Demographic and pregnancy outcome data for all 32 participants are shown in Table 1.

Table 1. Demographics and Pregnancy Outcome.

Variable	Category	Statistic/count
Total sample size	Pregnancy	32
	Postpartum	28
Sample size by ethnicity	Caucasian	29
	African American	1
	Hispanic	2
Sample size by delivery type	Vaginal: Natural	15
	Vaginal: Induction	9
	Unplanned Cesarean	8
Sample size by offspring gender	Female	16
	Male	16
Mean (SD) for demographic variables	Age	29.9 (4.1)
	Education (total years)	15.8 (2.2)
	Gestation period	275 (8.2)

SCL-90-R: Mean T-scores and other descriptive data for SCL-90-R are shown in Table 2. Mean SCL-90-R T scores across symptom clusters were not vastly different from normative mean for female non-psychiatric patient scores (29) and did not appear to show a significant trend from pregnancy to postpartum. However, the range of scores was substantial and thus, concealed the severity of distress experienced by some participants. In order to investigate this observation more thoroughly, the data

were re-analyzed *post hoc* to determine the number and percentage of women per symptom category with T-scores >60.

Table 2. Mean SCL-90-R scores by symptom cluster. Thirty-two subjects completed the instrument during pregnancy and 28 completed the instrument postpartum.

Category	Time	Mean	SD	Minimum	Maximum	Percent Symptomatic
Anxiety	Pregnancy	53.5	10.40	37	79	19
	Postpartum	53.8	11.63	37	80	32
Hostility	Pregnancy	56.3	6.89	42	74	25
	Postpartum	52.9	7.52	45	64	32
Phobia	Pregnancy	53.5	8.12	48	76	22
	Postpartum	56.5	8.77	48	76	39
Paranoia	Pregnancy	48.9	6.67	43	62	13
	Postpartum	47.8	6.08	43	66	4
Psychoticism	Pregnancy	52.1	6.98	47	71	19
	Postpartum	54.6	8.19	47	71	29
Somatization	Pregnancy	60.1	8.55	41	80	56
	Postpartum	55.4	10.44	35	80	36
Obsessions & Compulsions	Pregnancy	61.2	8.99	44	80	47
	Postpartum	58.0	9.95	37	80	43
Interpersonal Sensitivity	Pregnancy	55.1	7.18	39	69	31
	Postpartum	52.5	8.77	39	67	25
Depression	Pregnancy	60.4	5.86	51	71	50
	Postpartum	59.4	8.91	38	74	57
Global Severity	Pregnancy	58.8	7.23	46	76	44
	Postpartum	56.3	9.64	33	76	46

As can be seen in Table 2, we found measurable symptoms of depression in 50% and 57% of the participants pre- and postpartum. Obsessive-compulsive scores were also elevated at both test times but the percentage of women considered symptomatic declined from pregnancy to postpartum. As was expected, somatization scores were higher during pregnancy than following parturition.

Interestingly, mild to moderate psychotic symptoms were present in some women postpartum, absent concurrent elevations in paranoia. The most frequently ascribed to symptoms within the psychoticism cluster included fears of serious illness (n=8), loss of mind (n=7) and isolation (n=12). Three women exhibited distress regarding thought insertion and thought broadcasting, two were concerned about thought control and one woman indicated distress about auditory hallucinations.

Steroid Hormones: Descriptive data for pre- and postpartum hormone concentrations and changes from T1 to T2 are shown in Table 3. Consistent with the published research mean progesterone and estriol concentrations were elevated in late pregnancy and decreased markedly following parturition by 93% and 98%, respectively (30,31). Mean values for estrone and estradiol also followed expected trends (30,31) and decreased postpartum by 92% and 65% respectively, although within participant patterns were not uniform. Postpartum estradiol values increased rather than decreased in three participants and estrone concentrations increased in one participant.

Table 3. Salivary hormone descriptive statistics during pregnancy, postpartum, and change (pregnancy to postpartum). All hormone measurements are in pg/mL.

Hormone	Category	n	Mean	Median	SD	Minimum	Maximum
Progesterone	Pregnancy	31	1112.43	1184.80	555.61	221.60	2272.30
	Postpartum	28	80.89	79.50	36.65	20.30	176.10
	Change*	−: 27 +: 0					
DHEAS	Pregnancy	31	1089.16	884.10	1081.75	135.50	5774.00
	Postpartum	28	1462.4	1104.35	1062.17	449.10	4609.90
	Change	−: 6 +: 21					
Testosterone	Pregnancy	30†	37.48	27.95	29.86	2.60	94.30
	Postpartum	28	19.17	15.55	18.04	0.20	78.10
	Change	−: 21 +: 5					
Estrone	Pregnancy	31	37.57	34.80	13.60	1.70	72.50
	Postpartum	28	3.07	2.65	2.19	1.20	12.70
	Change	−: 26 +: 1					
Estradiol	Pregnancy	31	17.50	15.90	9.11	6.50	39.60
	Postpartum	28	6.08	3.20	6.52	0.60	28.30
	Change	−: 24 +: 3					
Estriol	Pregnancy	31	501.96	408.50	241.2	199.60	1003.90
	Postpartum	28	11.84	11.20	4.96	4.50	22.40
	Change	−: 27 +: 0					

*Changes are given as the number whose hormone concentrations increased (+) or decreased (−) from pregnancy to postpartum.
†One participant had a testosterone concentration below the detection limit.

Mean values for testosterone decreased an average of 49% following parturition, but individual patterns were atypical. We observed unexpectedly low late pregnancy testosterone concentrations, with eight participants showing testosterone concentrations below 10pg/mL. Following parturition, testosterone values increased in five participants and decreased in the remaining 21 participants.

Conversely, mean DHEAS concentrations were elevated at 37 weeks of pregnancy with a further increase of 35% following parturition. This trend was not consistent across all participants. When individual concentrations were examined, DHEAS increased for 21 (78%) of the 27 women following parturition. Whether or not the observed patterns of perinatal testosterone and DHEAS concentrations are consistent with published reports is difficult to ascertain because so few investigators have measured these hormones across pregnancy/postpartum and of those who have, test times and study populations differ significantly (32,33,34).

Hormone to Mood Associations: Pearson correlations were calculated for each hormone and SCL-90-R subscale and are listed in Table 4. No symptom clusters were correlated with progesterone, estrone or estriol either pre- or postpartum. While expected to be a close correlate of postpartum

psychiatric symptoms (6), estradiol was associated with very few symptom clusters in the present study. Postpartum estradiol was positively associated with increased postpartum phobia and interpersonal sensitivity whereas low prenatal estradiol was associated with an increase in the GSI, but not with any specific psychiatric symptom.

Table 4. Correlations between hormone levels (Pre-H = during pregnancy; Post-H = postpartum) and SCL mood states (Pre-M = during pregnancy; Post-M = postpartum). Significance is indicated as: *p < .05, **p <.01 and ***p<.001.

Category	Correlation	Progesterone	DHEAS	Testosterone	Estrone	Estradiol	Estriol
Anxiety	Pre-H & Pre-M	-0.062	0.228	-0.310	-0.033	-0.216	-0.236
	Pre-H & Post-M	0.206	0.042	-.469*	0.057	-0.373	-0.026
	Post-H & Post-M	0.262	.461*	-0.052	0.242	0.238	0.239
Hostility	Pre-H & Pre-M	-0.154	0.283	0.081	-0.167	-0.021	-0.129
	Pre-H & Post-M	0.175	0.173	-.609***	0.120	-0.316	-0.074
	Post-H & Post-M	0.199	0.358	-0.209	0.243	0.318	0.283
Phobia	Pre-H & Pre-M	-0.109	0.284	-.384*	0.189	0.035	-0.131
	Pre-H & Post-M	-0.009	0.168	-0.358	0.009	-0.164	-0.189
	Post-H & Post-M	0.227	.472*	-0.012	0.343	.482**	0.281
Paranoia	Pre-H & Pre-M	-0.093	0.366*	-0.326	0.227	-0.028	-0.069
	Pre-H & Post-M	-0.060	0.330	-0.251	0.003	-0.103	-0.032
	Post-H & Post-M	-0.080	.441*	-0.108	0.263	0.360	0.231
Psychoticism	Pre-H & Pre-M	-0.094	.376*	-.410*	0.154	0.033	-0.220
	Pre-H & Post-M	0.110	0.208	-.411*	-0.082	-0.055	-0.155
	Post-H & Post-M	0.150	.541**	-0.042	0.254	.329	0.267
Somatization	Pre-H & Pre-M	0.169	0.102	-0.445*	-0.034	0.029	0.072
	Pre-H & Post-M	0.290	0.089	-.497**	0.067	-0.334	0.191
	Post-H & Post-M	0.216	.508**	0.092	0.259	0.058	0.363
Obsessions & Compulsions	Pre-H & Pre-M	-0.029	0.134	-0.235	-0.097	0.094	-0.103
	Pre-H & Post-M	0.109	0.055	-.589**	-0.063	-0.301	0.106
	Post-H & Post-M	0.167	0.330	-0.081	0.137	0.234	0.109
Interpersonal Sensitivity	Pre-H & Pre-M	0.138	0.190	-0.264	-0.137	-0.212	-0.154
	Pre-H & Post-M	0.082	0.130	-.642***	-0.094	-0.330	-0.075
	Post-H & Post-M	0.132	-0.005	-0.306	0.032	.437*	0.116
Depression	Pre-H & Pre-M	-0.039	0.085	-0.335	-0.139	-0.094	-0.158
	Pre-H & Post-M	0.301	-0.018	-.471*	-0.162	-0.355	0.008
	Post-H & Post-M	.335	0.290	-0.084	0.149	0.175	0.232
Global Severity	Pre-H & Pre-M	-0.015	0.194	-.371*	-0.091	-0.081	-0.102
	Pre-H & Post-M	0.226	0.079	-.628***	-0.093	-.422*	0.053
	Post-H & Post-M	0.289	.387*	-0.082	0.182	0.268	0.281

Lower prenatal testosterone concentrations were significantly associated with a variety of prenatal psychiatric symptoms including phobia, psychoticism, somatization, and an increase in the GSI (p<.05 for each). Interestingly, low prenatal testosterone concentration was also a strong predictor and significantly associated with the development and/or exacerbation of a broad range of postpartum symptoms including anxiety, hostility, psychoticism, somatization, obsessive compulsive behavior, increased interpersonal sensitivity, and depression along with an increase in the GSI (p<.05 for each). Postpartum testosterone concentrations were not correlated with postpartum psychiatric symptoms.

Elevated prenatal DHEAS concentrations were associated with increased prenatal paranoia and psychoticism scores (p<.05 for both). As DHEAS concentrations increased postpartum, the number and strength of associations with psychiatric symptoms also increased. Postpartum DHEAS concentrations were significantly correlated with postpartum anxiety, phobia, paranoia, psychoticism, somatization and the GSI (p<.05 for all).

The comparisons between hormone concentrations of symptomatic and asymptomatic participants demonstrated no significant patterns for progesterone, estrone, estradiol or estriol. They did, however, reveal that each of the 14 women with late pregnancy testosterone concentrations <60 pg/mL experienced postpartum psychiatric disturbances (p=.002). Conversely, participants with pregnancy testosterone concentrations >60pg/mL demonstrated only minimal or no postpartum distress and those with testosterone concentrations >75pg/mL had positive psychiatric outcomes following parturition. The cutoff value for prenatal testosterone of <60 pg/mL represented an observed and natural pattern in the data.

Each of the women (n=4) with postpartal DHEAS concentrations >2500 pg/mL had late pregnancy testosterone concentrations < 60pg/mL and had significant postpartal psychiatric disturbances (p=. 028, P= .012, respectively) across multiple symptom domains. Figures 1 and 2 illustrate the relationships between late pregnancy testosterone, postpartal DHEAS and the number of SCL-90-R postpartum symptom scales >60. Salivary DHEAS values >2500 pg/mL are suspected of representing adrenal dysfunction for non-pregnant, non-postpartum women per laboratory reference ranges. This value has not been confirmed for pregnant/postpartum women.

Figure 1. Relationship between prepartum testosterone concentrations and total number of SCL-90-R symptom clusters with scores >60.

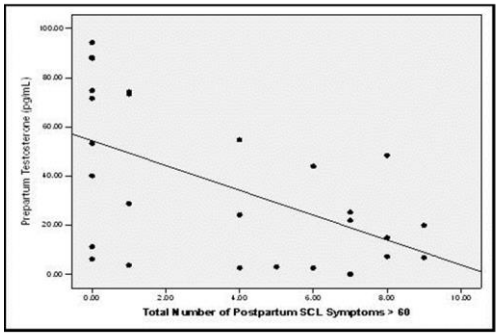
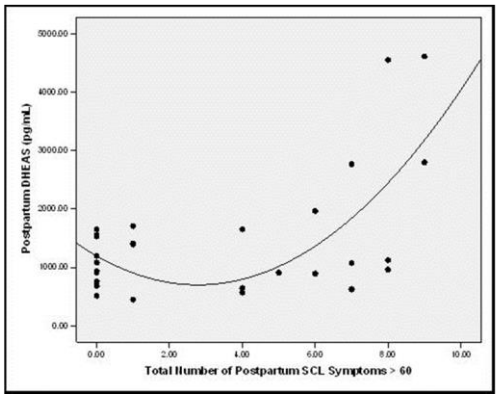


Figure 2. Relationship between postpartum DHEAS concentrations and total number of postpartum SCL-90-R symptom clusters with scores >60.



Discussion

While a preliminary investigation with a limited number of participants, results from this study nevertheless provide three important insights regarding perinatal mood disturbances. First, a significant number of women experience psychological distress beyond that commonly associated with the term "baby blues" and across a broader range of symptoms than generally expected from postpartum depression.

Fully 50% of the women experienced postpartum distress in four or more symptom areas, with both somatic and anxiety clusters core components of this distress. These results are consistent with investigations that have looked beyond postpartum depression and have found anxiety to be as or more prevalent than depression (35,36,37). In addition to increased anxiety-type symptoms, some women exhibited increased distress regarding psychotic symptoms. These symptoms were not accompanied by concomitant increases in paranoid ideation, but were concurrent with elevations across the spectrum of anxiety type disorders, suggesting perhaps a more agitated form of puerperal psychological distress than has been typically investigated.

Secondly, these data provide reasonably convincing evidence that the observed disturbances were hormonally mediated, albeit not as has been customarily hypothesized. The prevailing research posits that postpartum depression is triggered by a hyper-sensitivity to the expected changes in gonadal hormones (38). As such, most researchers have investigated the relationships between progesterone, progesterone metabolites and estradiol or estriol and varying degrees of postpartum depression (9,10, 11, 12, 13,14,15,16). We found no such correlations between progesterone or estriol and any symptom measured by the SCL-90-R and estradiol was not a prominent factor in peripartal distress. These findings are consistent with a recent study showing no associations between these hormones and postpartum depression (17).

Thirdly, postpartum mood disturbances were indicated hormonally during pregnancy. In this investigation, the strongest predictor of postpartum distress was diminished antenatal testosterone. Each of the 14 women with antenatal testosterone concentrations <60pg/mL experienced postpartum psychiatric symptoms. Conversely, only two participants with antenatal testosterone concentrations above 60 pg/mL exhibited postpartal psychiatric symptoms. The remaining 10 women were completely asymptomatic. In addition to the diminished testosterone, four women, including two women with the most severe postpartum symptoms, exhibited both diminished antenatal testosterone followed by a substantial increase in postpartum DHEAS concentrations.

It is acknowledged that there are limited data regarding pregnancy/postpartum testosterone and DHEAS concentrations in serum and no data for salivary values. However, observed progesterone, estrone, estradiol and estriol concentrations measured in this cohort of healthy primigravids followed the expected trends and are consistent with the range of salivary values published in multiple studies (14,15,30,31). That progesterone, estrone, estradiol or estriol concentrations were not associated with symptoms as has been suggested historically, is also in line with the published literature, where these hormones have not been strongly associated with symptoms (17). To the extent that progesterone and estrogen values were consistent with published data, it is expected that androgen values observed in this cohort are also valid and represent a unique feature in the development of postpartum psychiatric distress.

The relationship between DHEAS and mental health is slowly being established in non-pregnant populations.

Clinical psychiatric reports suggest that abnormally elevated DHEA and/or DHEAS concentrations elicit symptoms of anxiety, mania and psychosis that are in some cases resistant to traditional therapeutic approaches and abate only when hormone concentrations are brought in check (22,23,24,25). Similarly, lower concentrations of DHEA have been linked to depression and malaise in the elderly (26) and also with increased negative mood symptoms in perinatal women (35). Though not always measured, elevated DHEAS is frequently associated with elevated DHEA and testosterone (39). In the present study, DHEA concentrations were not measured, but lower testosterone concentrations were observed, both during pregnancy and following parturition.

The putative mechanisms by which these hormones affect CNS activity are complex. DHEAS is an anxiogenic and pro-convulsant compound through its inhibition of $GABA_A$ chloride channels (21) and is also associated with increased DA and NE via tyrosine hydroxylase induction (40). Simultaneously, diminished testosterone likely compounds the excitatory actions of DHEAS, as testosterone has been shown to be a fairly potent peripheral calcium L-channel antagonist (41) and inhibits cortical glucocorticoid response via the inhibition of arginine vasopressin (42). Inasmuch as DHEAS and testosterone are capable of eliciting significant psychiatric disturbances by themselves, when superimposed upon the chronically elevated and precipitous decline of progesterone and estradiol associated with pregnancy and postpartum, symptom frequency and severity are likely to increase. This is particularly true for the anxiety related symptoms insofar as chronic progesterone exposure followed by rapid withdrawal diminishes GABAergic activity (43). A concurrent increase in DHEAS may further diminish GABAergic activity and heighten CNS excitability.

The postpartum reduction in estradiol, long suspected of moderating psychiatric symptoms through its broad excitatory influence across multiple neurotransmitter systems might also moderate symptoms indirectly through its influence on DHEAS concentrations. Researchers posit an association between estradiol and diminished sulfatase activity (44,45,46), a potential factor in the pattern of puerperal hormones observed in the present study. Reduced steroid sulfatase, because of its role in converting DHEAS to DHEA, the biologically active precursor to downstream androgens (androstenedione and testosterone) and estrogens, could be associated with elevated DHEAS and diminished testosterone concentrations. In hormone dependent cancer cells, researchers have shown that high concentrations of estradiol limit sulfatase activity and estrone concentrations, as part of a negative feedback loop that ultimately limits estradiol's own synthesis (44,45). Preliminary work with rodents demonstrates a clear relationship between the postpartum reduction in estradiol concentrations and an increase in both cortical DHEAS and a diminishment of sulfatase (46). Similarly, following the pharmacological reduction of sulfatase, researchers have noted increases in both DHEAS and psychological distress or agitation/aggression in cancer patients (47) and male rodents (48) respectively. In the present study, neither enzyme activity nor the concentrations of the other hormones along the androgen pathway were measured and thus hypotheses regarding mechanisms remain speculative. However, the unique pattern of hormone values and associations with psychiatric symptoms points to a possible biological component in the etiology of postpartum psychiatric disturbances.

Strengths and Limitations: Unlike most investigations of perinatal mood, the present study examined a broad range of psychiatric symptoms and wide selection of perinatal hormones. Where others have focused almost exclusively on postpartum depression and its connection to "feminine" hormones this study expanded the observation field to include nine common psychiatric disturbances and six hormones both of gonadal and adrenal origin. In order to capture the most significant changes in perinatal hormone concentrations and to detect distress early, we chose to test in late pregnancy and early postpartum and to control both the day and time of assessment as tightly as was reasonably practicable. These considerations allowed us to more fully characterize perinatal psychological and hormonal changes and to identify early markers of distress that had been previously un-documented.

There were, however, several limitations to the study. This was an initial investigation and as such our sample size was not only limited and but was demographically homogenous despite recruiting from both urban and suburban facilities. Our sample was older, predominantly Caucasian, and perhaps better educated than volunteers from other studies. Since age can be a factor in the measurement of hormone concentrations, and ethnicity may or may not be a factor, the observations from this cohort will require comparison with younger and older mothers from more diverse backgrounds. With respect to education level, though not likely to alter hormone values, it may impact the ability to articulate symptoms, particularly in an instrument such as the SCL-90-R that relies on self-report methodology. Moreover, the use of SCL-90-R, although well-validated when tracking change in

psychiatric symptomatology across time, does not provide diagnostic designations. Future investigations will need to employ standardized diagnostic instruments to determine which symptom clusters reach criteria. However, we were able to demonstrate significant associations with specific hormones and symptoms. This was unexpected given the small sample size in the present study, suggesting that the correlations found were not spurious and therefore warrant future investigation.

The use of salivary hormone assays versus serum assays was both a strength and weakness. Where hormone values measured from serum/ plasma represent the total concentration of circulating hormones, a significant portion of the hormone is bound to plasma proteins (49) and thus not in the biologically active form. Those measured from saliva represent only the unbound fraction of the hormone. Thus, hormones measured from saliva have been suggested to be a more accurate marker of the biologically active fraction of the hormone (50). While that point is still debated, the bound: unbound ratios in serum are believed to be in dynamic equilibrium. Thus, it is expected that any measurement of free hormone would have a consistent relationship to the total hormone concentrations, a finding that has been documented in a number of studies (51,52,53). However, methodological inconsistencies in salivary hormone research are common and procedural standardization between laboratories is limited (54). Moreover, there are no published reference ranges for salivary hormone concentrations across pregnancy or postpartum. Nevertheless, having employed rigorous controls in sample collection and measurement methods, we expect the results presented here to be validated by future research.

Conclusion: Results from this study strongly suggest that puerperal psychological disturbances may be more prevalent than previously estimated and appear to be driven more by anxiety and related symptoms such as obsessive compulsive, somatic complaints and sub-threshold psychotic symptoms than currently acknowledged. More importantly, however, these disturbances were not aberrant or excessive responses to expected postpartum transitions in progesterone, estradiol, estriol or estrone. Rather, the psychiatric disturbances observed in this cohort of healthy, primigravid women appeared to be mediated by perturbations in the adrenal androgen pathway. Diminished late pregnancy testosterone and elevated puerperal DHEAS were strongly correlated with both the number and severity of symptoms and could, with further testing, provide diagnostic utility for predicting, confirming and/or treating puerperal mental illness.

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