Prenatal Stress Disrupts Reproductive Behavior and Physiology in Offspring

LORRAINE ROTH HERRENKOHL

Psychology Department
Temple University
Philadelphia, Pennsylvania 19122

Stress and anxiety affect the developing organism at any stage of the life cycle. At any stage in development, biological, psychological, and social factors influence later reproductive behavior and physiology. The present paper examines the role of prenatal stress as a disruptive factor in reproductive psychophysiology. The theses are that stress has a critical impact on the developing organism during the prenatal stage, when the neural circuitry underlying later biochemical-behavioral events is laid down, and that because of this impact, prenatal stress negatively affects later behavior in lower animals and humans as well. The orientation owes much to Schneirla's concepts[1] of similarities and differences in levels of organization in behavior and stimulus-response relationships across the phyletic scale, from lower animals to humans. It also owes much to Rosenblatt[2,3] and his conception of stages in development and reciprocity in behavior between mothers and their young. Inspired by Rosenblatt, whose training was grounded not only in experimentation but clinical theory as well, I have extended my still-ongoing interest in hard science into the clinical field. A more fully developed rationale and data appear in Mathew's book, "The Biology of Anxiety."[4]

I define stress as any real or imagined trauma, physical or psychological, that leads to the release of stress hormones associated with the adrenal glands. The range of stress-inducing stimuli is varied. It differs from organism to organism, and not uncommonly within the same organism, depending upon circumstance and time. The range of stressful stimuli examined in the psychobiological literature has also varied. Stimuli range from animal models (employing discrete changes in environmental temperature or in dosages of stress hormones exogenously administered[5–8]) to human models such as those social psychologists employ to examine the effects of life situational stress (death of loved ones, moving, marital discord) on human health and behavior.[9,10]

Anxiety is the consequence of exposure to real or imagined stress. It is a state attributed to lower animals and to humans as well. On the human level, there are two major classes of clinical anxiety (according to the "Diagnostic and Statistical Manual of the American Psychiatric Association," 3rd edit., 1980). One class includes anxiety disorders of childhood or adolescence such as overanxious disorders and separation anxiety disorders. The second class is the adult category which includes phobias, generalized anxiety reactions, panic anxiety reactions, and post-traumatic stress disorders. Some behavioral manifestations of anxiety include extremes in behavior: irritability, hyperactivity, panic, hyperattentiveness, and obsessive-compulsive

reactions at one end and social withdrawal, apathy, and sadness at the other. In animal studies, anxiety has been examined in paradigms such as conditioned anxiety.[11]

CLASSIC COMPARATIVE AND PHYSIOLOGICAL PSYCHOLOGY

Prenatal maternal stress has been related to neonatal activity and irritability in lower animals and humans in documented research for the past 30 years. A classic conditioned anxiety experiment was performed by Thompson in 1957.[11] Female rats were trained in a double-compartment shuttle box first to expect strong shock at the sound of the buzzer and then to avoid the shock by opening the door between the compartments and running through to the safe side. When they had learned the task, they were mated. As soon as they were pregnant, the animals were exposed to the buzzer in the shock side of the shuttle box but with the shock turned off and the door to the safe side locked. Therefore, during gestation, the animals were exposed to "expected," not real, shock. Emotional characteristics of the offspring were compared at two later stages of development. Experimental animals showed a much higher latency of activity than control animals at both ages of testing in an open field test where measures of amount of activity and latency were recorded. Moreover, experimental animals were slower to leave the home cage ("more fearful") than controls at the first age of testing. On the basis of his findings, Thompson believed that stress hormones coursing through the mother's blood affected the developing fetus and that these hormones produced the behavioral differences. He had no direct evidence for this effect.

In the decade that followed Thompson's research,[11] many others studied the influence of maternal stress on later offspring behavior.[12–18] The implicit mechanism in all that research involved the sharing of stress hormones by the mother and fetus via a common blood supply, but no direct evidence was collected in support of that view.

CLASSIC DEVELOPMENTAL PSYCHOLOGY

Experiments in developmental psychology also illustrated the impact of maternal stress on the offspring. Lester Sontag, long an important figure in child development at the Fels Research Institute, studied pregnant women undergoing stress. Sontag reported findings of the Fels Research Institute for the study of human development in the years from 1932 to 1966.[19–21] Research was designed to explore the behavior of the human fetus, its developmental progress and individual differences, perceptions, capabilities, and responses to stimuli during the last months of pregnancy. Sontag[19] observed infants of mothers who had undergone severe emotional stress during the latter part of their pregnancies. He perceived that behavior patterns during gestation carried over into neonatal life. Sontag[19] reported that fetuses of mothers undergoing stress responded with large increases in sharp or irritable body movements, presumably the result of changes in the constituents of the mothers' blood. After birth, these infants remained irritable and hyperactive for weeks or months. They cried a great deal and slept for short periods only. Most of these infants exhibited a food intolerance

and frequent or often loose stools, suggesting an autonomic or psychosomatic component of prenatal stress exposure as expressed in gastrointestinal function. Moreover, they regurgitated much of their food and frequently were switched from one formula to another without significant improvement. They failed to gain weight for a long time.

Sontag was able to correlate verbal reports by the mothers on fetal activity with kymographic records. The mothers were asked to lie on cots in the laboratory. Inflatable bags were placed over each quadrant of their abdomen. When the fetus kicked, there were pressure changes in the inflatable rubber bags which in turn were recorded by a kymograph. By this procedure and by taking advantage of spontaneously occurring natural events in the mothers' lives, Sontag was able to collect information on responses of the fetus to stress. A case is given below:

> In one instance a young woman carrying her baby, which we had been studying weekly in terms of activity and heart rate level, took refuge at the Fels Institute building one evening because her husband had just suffered a psychotic break and was threatening to kill her. She was terrified, felt alone and did not know where to turn for help. She came to the Institute, and we gave her a bed and room for the night. When she complained after a few minutes conversation that the kicking of her fetus was so violent as to be painful, we proceeded to record the activity level. It was more than 10-fold what it had been in the weekly sessions prior to this incident. Another case came to our attention when a woman we had been studying lost her husband in an automobile accident. Again, the violence of the activity and the frequency of movement of the fetus increased by a factor of more than 10. During the period of 10 years, we managed to collect 8 such dramatic incidences, all showing the same phenomena of extreme increase in fetal activity in response to grief, fear and anxiety. Children of such mothers, who suffered their emotional trauma late in pregnancy and not early, showed, of course, no congenital defect. In general, they were, however, irritable, hyperactive, tended to have frequent stools and 3 of them had marked feeding problems. (Sontag, 1966, Reference 21, p. 784.)

Later Stott[22] in Scotland reported the findings of a follow-up study from birth to the fourth year of life of the effects of prenatal stress on a sample of 200 infants. By using medical records and interviews by health nurses in the home, Stott[22] drew impressive profiles of the impact of prenatal stress on later health and behavioral development.

The types of child morbidity Stott[22] associated with personal tensions in pregnancy included physical illness (twice as much eczema and middle ear infections, somewhat more bronchitis, and severe respiratory trouble); minor physical and functional abnormalities (small size, profuse sweating, flushing, or choking); developmental difficulties (twice the incidence of late walking or poor walking such as flat-footed or clumsy, some speech defects); and behavioral abnormalities (twice as many entries for fretful, whimpering, restless, or clinging behaviors). Ten of the 14 cases had one or more indications of behavioral disturbances characteristically associated with congenital hyperactivity.

Stott's[22] most striking finding was that marital crisis during pregnancy produced the highest child morbidity scores. A case involving marital discord during pregnancy which produced a high child morbidity score is described below:

> Marital relationship is not good. There has been frequent quarreling all through the marriage. The husband is reputed to be a heavy drinker, particularly at weekends when he is very abusive and often puts the wife out of the home. He is, however, a good worker (on constant night shift) and supports his wife and family fairly well. There is nevertheless,

> signs that the family may break down completely. The night before the birth there had been a violent quarrel with husband. (Stott, 1973, Reference 22, p. 776.)

By the mid-1970s therefore, a body of evidence had developed that maternal stress negatively influences subsequent health and behavior of offspring. Significant parallels in maternal stress effects on offspring were apparent in laboratory animals and humans.

CONTEMPORARY PRENATAL STRESS RESEARCH

Recent advances in prenatal stress research have been marked by the quest for an underlying mechanism. In interdisciplinary research, psychologists studying hormones and behavior have collaborated with biologists, endocrinologists, and biochemists to attempt a unified approach to the study of maternal stress on offspring.

One current model of prenatal stress research employs sexual differentiation of the brain. The sexual differentiation model of the brain states that the hormonal milieu, not the genome, determines sexual dimorphism in an inherently female brain.[23] Normal patterns of sexual behavior and gonadotropin secretion are established by adulthood as a function of the presence or absence of androgens during critical perinatal sexual differentiation stages. Two lines of evidence support this view: chemical or surgical castration of genetic males during perinatal life feminizes and demasculinizes reproductive functions; and exposure of genetic females to androgens during a critical developmental stage masculinizes and defeminizes reproductive physiology, morphology, and behavior. The severity of the masculinizing and defeminizing action of perinatal androgens (particularly its potent metabolite estradiol) depends upon the amount and timing of the hormone.[23]

The possibility that maternal stress can influence sexual differentiation was stimulated by Ward's discovery[24] that prenatal stress feminizes and demasculinizes sexual behavior in males. She exposed rats in late pregnancy to the stress of heat, restraint, and bright lights three times daily during the last trimester of gestation and reported that by adulthood the offspring showed a significant reduction in the percentage of stressed males that copulated and ejaculated compared to control males, and a significant increase in lordotic performance. She believed that the prenatal stress syndrome in males, characterized by diminished copulatory patterns and increased lordotic behavior potentials, developed from diminished exposure of fetal males to gonadal androgens, presumably as a result of increased exposure to stress steroids.[24] She also believed that parallel influences might be a cause for homosexuality in men.[25]

Moyer *et al.*[26,27] have suggested that prenatal stress may modify the neuroanatomical and biochemical organization of the brains of both males and females and turn the direction of male fetal brain development toward that of the female sex. They combined the microdissection procedure of Palkovits[28] for removing individual brain nuclei with sensitive radioisotopic enzymatic assays for norepinephrine (NE) and dopamine (DA). In pregnant mothers, Moyer *et al.*[26] discovered that stress during pregnancy reduced steady-state levels of NE in brain regions associated with gonadotropic secretion. The major noradrenergic pathway that underwent change during stress was the ventral ascending bundle (i.e., the medial preoptic nucleus, anterior hypothalamus, and median forebrain bundle). They also reported that the locations of DA decreased as a function of prepartal stress and overlapped with those brain regions in which catecholamine (CA) depletions have been implicated in functional affective disorders in humans.

They postulated that the relatively high incidence of certain mental disorders when sex steroids and CA fluctuate widely (as during diestrus, the postpartum period, and at menopause) suggests an interrelationship among female hormones, CA, and psychological state. Stress during pregnancy with corresponding changes in brain monoamines may set the stage for postpartum disorders.

Moyer *et al.*[27] also examined the effects of prenatal stress on CA concentrations in the brains of the male and female offspring as adults. The major pattern of brain change in male offspring was similar to that in stressed mothers. The major system that underwent change involved NE, the major direction of change was a decrease, and the major brain regions that underwent change were those associated with gonadotropic secretion from the anterior pituitary gland and with the regulation of sexual behavior. They postulated that decreases in brain NE may be the basis for the feminized and demasculinized sexual behavior of males.[24]

Among the most interesting findings was the observation that prenatal stress markedly affected CA concentrations in female offspring. Prenatal stress increased the steady-state concentration of DA in the hypothalamic arcuate nucleus of stressed female offspring by 153%! Because marked alterations in arcuate DA have been associated with abnormalities in the release of gonadotropic hormones from the anterior pituitary gland, it was predicted and ultimately observed that prenatal stress would produce reproductive dysfunctions in female offspring.[5,29]

Herrenkohl[5] exposed pregnant rats to restraint-heat stress during the last trimester of pregnancy and examined female offspring for reproduction function in adulthood. Pregnant rats were restrained in 18 × 8-cm semicircular Plexiglas cages under four bright incandescent lights. The procedure caused a surface illumination of 400 ft-cd and a surface temperature of 34°C. This was the standard restraint-heat stress procedure in all of Herrenkohl's experiments. Stress sessions occurred from day 14 to day 21 of gestation three times daily for 45 min starting at 10 AM with alternating 45-min periods of rest in the home cage. Nonstressed mothers remained unhandled. When compared to nonstressed female offspring, stressed female offspring exhibited higher incidences of estrous cycle disorders, spontaneous abortions, and vaginal hemorrhages.[5,29] They also had higher incidences of stillbirths and neonatal mortalities in a subsequent generation of progeny (TABLE 1). Cross-fostering procedures between and within treatment groups ruled out the possibility that prepartal-stress-induced disturbances during the postnatal period were the primary causes of the reproductive deficits in the offspring.[5,30] Prenatal stress by itself markedly reduced fertility and fecundity in female offspring.

Recent experiments have found that maternal stress changes testicular (Leydig cell) and brain steroid aromatase activity in rat fetuses in patterns similar to those alterations in fetal testosterone levels.[31,32] It has also been reported that maternal stress differentially alters pituitary, gonadal, and adrenal function in rats and mice.[6–8,33,34]

Critical issues remaining in the field involve answers that reconcile apparent contradictory results. For example, with regard to stressed male offspring, Ward[24] has found both a demasculinization and feminization of sex behavior (decreases in copulatory performance and increases in lordosis), whereas Whitney and Herrenkohl[35] have reported only behavioral feminization. Also in a "replication" of Herrenkohl's experiments,[5] Beckhardt and Ward[36] found that reproductive functioning in prenatally stressed female offspring remained intact. Such inconsistencies may be explained by differences in strain of animal, rearing conditions, and/or experimental procedures. Ward, for example, characteristically uses only 200 ft-cd of light stress,[24,36] whereas Herrenkohl uses twice as much.[5,29]

A final issue remaining is the mechanism of prenatal stress. In an experiment with the endocrinologist Weisz, Ward presented evidence that maternal stress altered plasma

testosterone in fetal males.[31] They employed radioimmunoassay to measure plasma testosterone in cesarean-delivered normal and stressed fetal males during the last trimester of pregnancy. In normal males a surge of plasma testosterone characteristically occurred on the 18th or 19th gestational day. This testosterone surge occurred prematurely in the stressed male, on gestational day 17. On this basis, Ward and Weisz[31] concluded that the central nervous system (CNS) of fetal males becomes demasculinized and feminized, not as a result of decreased exposure in absolute amount of circulating testosterone during the late gestational stage, but because there is a desynchrony between the maturational stage of the CNS and patterns of testosterone secretion during fetal life.

The most parsimonious explanation with respect to female offspring is that the prenatal stress syndrome in females may result from exposure to increased androgens. The source of the androgens might include: (a) the fetal adrenals: restraint-heat stress elevates maternal body temperature and thereby may affect the fetus directly[37]; (b) the maternal adrenals: restraint-heat stress produces maternal pathology and adrenocortical response; and/or (c) the fetal testis: this intriguing possibility is suggested by the observation that masculinization of fetal females can be mediated by proximity to fetal males.[38,39]

TABLE 1. Summary of Effects of Prenatal Stress on Fertility and Fecundity in Female Rat Offspring in Five Experiments[a]

Female Offspring	*N*	Percentage Pregnant	Percentage Giving Birth	Percentage of Stillbirths	Percentage of Neonatal Deaths	Percentage of Litters Intact
Prenatally stressed	274	39 **	22 *	21 **	37 **	42 **
Nonstressed	303	89	86	5	2	93

[a] Some of the data presented were taken from Herrenkohl.[5]
*$p < 0.01$.
**$p < 0.001$.

CURRENT SOCIOCLINICAL RESEARCH

In one kind of newly emerging research strategy, psychobiologists are adapting socioclinical research to issues of stress and reproductive dysfunction in women. In one of these studies, Herrenkohl is examining the relationships among stress, personality, mood, and menstrual distress. Preliminary findings support the hypothesis that prenatal stress may affect personality, mood, and menstrual activity in women. The following observations pertain to several samples of women questioned retrospectively about the incidence of life situational change (as measured by the Holmes-Rahe Social Stress Scale) over four stages of the life cycle (Prenatal Stage, Early Childhood, Adolescence and Young Adulthood, Adulthood):

1. The higher the Prenatal Stress score (death of loved one, moving, marital discord), the higher the Menstrual Distress score (Moos Menstrual Distress Questionnaire).

2. The higher the Prenatal Stress score, the more masculine the social self-perception (Bem Androgyny Scale).
3. The higher the Early Childhood Stress score, the more irregular the menses.
4. The higher the Adolescence and Young Adulthood Stress score, the more masculine the social self-perception.
5. The higher the premenstrual distress, the higher the anxiety, depression, and neurotic symptomology (Beck Anxiety Checklist, Beck Depression Inventory, Hopkins Self-checklist).

Currently we are gathering evidence on the interrelationship of prenatal stress, premenstrual syndrome, and postpartum depression. We are also formulating hypotheses on mechanisms by which psychosocial stress may affect the developing reproductive substrate and later behavior.

We are also trying to tap the information bank that exists at the National Institute of Neurological Diseases and Strokes. It has a massive compilation of data from a collaborative perinatal study on over 10,000 women and their pregnancies. The study examines the relationship between prenatal conditions (personal circumstances, drugs, health) and outcomes for the offspring (neonatal health, neurological development, school performance). From some of the findings to date,[40] it is already possible to note that relationships exist between marital status during pregnancy and survival and health of offspring. The incidence of neonatal deaths and neurological impairment among infants is extraordinarily high among widows (Reference 40, pp. 54, 57), suggesting that the prenatal trauma associated with the death of the husband had deleterious and far-reaching consequences for the offspring. Also, the incidence of low-birth-weight young was high among nonmarried women (Reference 40, p. 55). Is there a relationship between prenatal maternal stress and reproductive dysfunction in the daughters?

Laukaran and van den Berg[41] have already found that negative maternal attitudes toward pregnancy deleteriously influence offspring outcome and obstetrical complications. Tapping an already-existing data bank on 8000 or so women at the Kaiser Permanente Foundation in the San Francisco Bay area, they controlled for such factors as socioeconomic class, maternal health, and nutrition. They concluded that the single major factor associated with postpartum infection and hemorrhages, and deaths and congenital abnormalities in newborns, was a negative maternal attitude toward having the baby. This was probably due to "stress-mediated change in hormones." There is also evidence that prenatal loss of father elevates the incidence of psychiatric disorders in adulthood.[42]

SUMMARY AND CONCLUSIONS

Prenatal maternal stress has been related to neonatal activity and irritability in both lower animals and humans in documented research for at least the past 30 years. Contemporary animal research demonstrates that prenatal stress feminizes and demasculinizes the sexual behavior of males and reduces fertility and fecundity in females, producing estrous cycle disorders, spontaneous abortions, or vaginal hemorrhaging and high neonatal mortality. Mechanisms of stress are being sought in the maternal-fetal blood exchange, hormonal alterations in the hypothalamus-pituitary-gonads and adrenals, and in brain catecholamines.

Contemporary human research demonstrates that negative maternal attitudes toward pregnancy are related to high incidences of congenital abnormalities and infant deaths. Severe psychosocial stress is related to high incidences of neonatal deaths and neurological impairments in infants, and a high incidence of psychiatric disorders in adulthood. Data derived from both animal and human research may help explain the etiology and mechanisms of prenatal-stress-induced reproductive dysfunctions as well as some forms of human psychopathology.

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