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# Prenatal Stress: A Predictor of Childhood Behavior Disorders

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# Prenatal Stress: A Predictor of Childhood Behavior Disorders

## Abstract

**Background:** Behavior disorders in children are disruptive to the lives of those who are close to the child and can affect life in the home, school or social setting. One theory is that maternal prenatal psychosocial stress can potentiate such disruptive behavior. Several animal studies have found a correlation between prenatal stress and child development. This systematic review evaluates observational studies of prenatal psychosocial stress in humans and the behavior of their offspring. Does psychosocial stress in pregnant mothers lead to behavior disorders in their children?

**Method:** An extensive search of medical literature was conducted using databases of Medline Ovid, Web of Science, CINAHL, and Google Scholar using the keywords: child behavior disorders, life change events, pregnancy and psychosocial stress. Studies meeting exclusion and inclusion criteria were evaluated for quality using the GRADE system.

**Results:** Three observational studies were thoroughly evaluated and are included in this review. One study found a correlation between prenatal stress and temperament and problem behaviors of toddlers. One study suggests evidence supports a link between prenatal bereavement and the development of ADHD in offspring. One *in vitro* fertilization study examined the nature vs. nurture question by comparing genetically related mothers to genetically unrelated mothers, and assessing the correlation between prenatal stress and behavior problems of their offspring.

**Conclusion:** Each study suggests the correlation between prenatal psychosocial stress and behavior disorders in children but each study has some level of limitation leading to inconclusive evidence. Understanding the correlation between prenatal stress and child behavior, medical providers could aid in preventing the behavior problems. Identifying those mothers who are stressed and providing them with resources to alleviate the stress could potentially mitigate the undesired behavior in the child. More studies are needed to examine the theory that prenatal stress effects behavior development in children.

## Degree Type

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child behavior disorders, life change events, pregnancy and psychosocial stress

## Subject Categories

Medicine and Health Sciences

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**Prenatal Stress:  
A Predictor of Childhood Behavior Disorders**

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A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 10, 2013

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## Biography

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Robyn Trasen grew-up in Denver, Colorado. She earned a Bachelor of Science degree from Colorado State University in Fort Collins, Colorado, in 1995, with a major in Human Development and Family Studies. While in college she pursued an EMT-B certification which enabled her to work in a skilled nursing facility in New Mexico. It was there that she discovered her desire to work in a geriatric community. In 1998, Robyn and her husband moved to Oregon where she worked for several years in an assisted living facility. After taking some time to raise a family, Robyn decided to pursue a career as a physician assistant combining her interest in geriatrics and her passion for patient care.

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## Abstract

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**Keywords:** child behavior disorders, life change events, pregnancy and psychosocial stress

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# Table of Contents

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|  |    |
|--|----|
| Biography .....                                    | 2  |
| Abstract .....                                     | 3  |
| Acknowledgements .....                             | 4  |
| Table of Contents .....                            | 5  |
| List of Tables.....                                | 6  |
| List of Abbreviations.....                         | 6  |
| BACKGROUND.....                                    | 7  |
| METHODS.....                                       | 9  |
| RESULTS.....                                       | 10 |
| DISCUSSION .....                                   | 16 |
| CONCLUSION.....                                    | 21 |
| References .....                                   | 23 |
| Table I: Characteristics of Reviewed Studies ..... | 25 |

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## List of Tables

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Table I: Characteristics of Reviewed Studies

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## List of Abbreviations

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|            |  |
|------------|--|
| ADHD.....  | Attention Deficit Hyperactivity Disorder                           |
| CI.....    | Confidence Interval  |
| EHR.....   | Electronic Health Record   |
| GRADE..... | Grading of Recommendations, Assessment, Development and Evaluation |
| HPA.....   | Hypothalamic-Pituitary-Adrenal                                     |
| HR.....    | Hazard Ratio   |
| IVF.....   | <i>in vitro</i> fertilization                                      |
| MeSH.....  | Medical Subject Heading  |
| NIMH.....  | National Institute of Mental Health                                |
| OR.....    | Odds Ratio   |

# **Prenatal Stress: A Predictor of Childhood Behavior Disorders**

## **BACKGROUND**

Problem behaviors and difficult temperament in children are often typical, transient and a part of growing up. When these behaviors extend beyond the length of time of a typical developmental phase and disrupt a family or educational environment, parents or guardians often seek help from their medical providers.

Behavior disorders extend beyond typical disruptive behavior or temperament. Huizink et al<sup>1</sup> classifies difficult temperament in three broad categories: difficult or negative mood, inability to easily adapt to new people or situations, and short attention span. According to the Substance Abuse and Mental Health Services Administration, a behavior disorder is defined by the length of time the child exhibits hostile, disruptive, or aggressive behavior. The behavior problem becomes a disorder when the child exhibits the behavior for more than six months.<sup>2</sup> Examples of such behaviors are repeated, uncontrolled tantrums, violence or the threat of violence to animals and people, physical destruction of property, theft and dishonesty. An estimated 16% of children have a development or behavior disorder.<sup>3</sup>

Attention Deficit Hyperactivity Disorder (ADHD) is one such behavior disorder. It is estimated that ADHD is diagnosed in 3-5% of United States children.<sup>4</sup> According to the National Institute of Mental Health (NIMH), an ADHD diagnosis is made when a child exhibits inattentive, hyperactive, or impulsive behaviors for more than six months.<sup>5</sup> ADHD often potentiates difficulties in school, home and social settings.

Finding a root cause to the behavior is the key to understanding and preventing the undesired behavior of the child. One theory is that maternal prenatal psychosocial stress can produce disruptive behavior in offspring.<sup>6</sup>

Psychosocial stresses, also referred to as life change events, are incidents which cause the individual to alter their typical life routine, behaviors, or emotions.<sup>7</sup> According to the Holmes and Rahe Social Readjustment Rating Scale, some examples of life event stressors are the death of a family member or friend, marital issues, job transitions, a change in financial status, or a change in living conditions.<sup>8</sup>

Animal studies show that offspring are negatively impacted by prenatal stress. In 1992, Schneider et al<sup>8</sup> of the University of Wisconsin-Madison presented findings that infant monkeys exposed to prenatal psychological stress display both impaired attention span and negative emotional responses to difficult situations.<sup>8</sup>

In 1996, Barbazanges et al<sup>10</sup> presented data in the Journal of Neuroscience connecting maternal stress and the development of the hypothalamic-pituitary-adrenal (HPA) axis in offspring. High levels of maternal glucocorticoids in rodents negatively effect mood and emotions, and leads to other stress-related outcomes in offspring.<sup>10</sup>

Marta Weinstock of Hadassah Medical Center presented experimental data of monkeys and rodents in 1997 which supports the claim that offspring exposed to prenatal stress exhibit an inability to cope in adverse situations. She added that these offspring also exhibit fearful behaviors.<sup>11</sup>

In 2004, Janet DiPietro of Johns Hopkins University reported that the stress endured by restrained lab animals produced undesired behaviors in offspring such as an inability to appropriately handle stressful situations.<sup>6</sup>

Evidence in these animal studies suggests a correlation between prenatal stress and behavior in offspring. The focus of this review is to thoroughly evaluate studies which attempt to correlate prenatal psychosocial stress to childhood behaviors in humans. Does psychosocial stress in pregnant mothers lead to behavior disorders in their children?

## **METHODS**

An extensive search of medical literature was conducted using databases of Medline Ovid, Web of Science, CINAHL, and Google Scholar. The initial search of cohort studies was conducted using the Medical Subject Heading (MeSH) terms: child behavior disorders, life change events, pregnancy and psychosocial stress. Human studies including specific stressors such as mothers who experienced bereavement while pregnant and the effect on the offspring with regard to specific behavior disorders such as ADHD were included in the search.

The search was narrowed further by excluding animal studies and studies in countries dissimilar to the United States. In order to focus specifically on psychosocial stress, studies that evaluated physical stress associated with medical conditions or illicit drug use during pregnancy as well as previously diagnosed psychological disorders in mothers, such as anxiety and depression, were excluded. Studies which evaluated cognitive and learning dysfunction in children as outcomes were also excluded.

Studies that met inclusion and exclusion criteria, were evaluated for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.

## **RESULTS**

After excluding non-English language and duplicate studies, the initial search yielded 85 articles. Three studies met inclusion and exclusion criteria and were included in the review. Each study reports some degree of correlation between psychosocial stress of mothers, endured during pregnancy, and the behavior of their offspring. See Table I.

### **Study 1: The effects of prenatal stress on temperament and problem behavior of 27-month-old toddlers, Gutteling et al**

This 2002 multi-phase prospective longitudinal study<sup>12</sup> evaluated the behavior of children who were exposed to prenatal stress *in utero*. Behavior evaluations were conducted at 3 months, 8 months and 27 months of age. This systematic review evaluates the third phase, conducted in 2004, the behavior of the 27-month-old toddler.

Included in Study 1<sup>12</sup> were the offspring of nulliparous women in the Netherlands who were pregnant with one fetus. Those excluded from the study were non-Dutch speaking mothers, pregnancies of less than 37 weeks gestation, major pregnancy or birth complications, an Apgar score less than 7, poor health of the infant and pregnancies in which mothers used illicit drugs or medications that posed a risk to the fetus.<sup>12</sup>

After exclusion criteria were met, there were 630 eligible candidates for the study. The parents of 400 of these children declined participation due to the length of time

required to complete the study. After further exclusions due to stillbirths, multiple births, pregnancy complications, and drop-outs due to personal reasons (disinterest, lack of time, and relocation), 170 infants were evaluated in the early phases of the study, at 3 and 8 months of age. For the third phase of the study, several other participants were excluded due to medical reasons and death, leaving 140 eligible participants of which 119 parents agreed to continue the study to the child's age of 27 months. However, of those 119 participants, 16 had incomplete data, specifically, cortisol levels were not recorded. Therefore, the authors report in the abstract that 103 healthy toddlers remained in the study.<sup>12</sup>

The study methods consisted of questionnaires of the pregnant mothers, a parent questionnaire about the behavior of their toddler, and an observation of toddler behavior by trained psychologists who were blinded to the questionnaires. To measure the stress of the mother, the participants completed three questionnaires at each stage of their pregnancy, in the first, second and third trimesters. The first questionnaire evaluated the mother's pregnancy anxiety using the Pregnancy Related Anxieties Questionnaire-Revised.<sup>1</sup> The questionnaire included questions about the mother's fear of giving birth, fear of bearing a physically or mentally handicapped child, and concerns about her own appearance. The second questionnaire measured perceived stress using Cohen and Williamson's Perceived Stress Scale.<sup>13</sup> The third questionnaire was a measure of "daily hassles" using the Everyday Problem List.<sup>1</sup>

Several potential covariates were examined and factored into the statistical analysis. Some of those covariates were maternal age, smoking behavior, use of alcohol during pregnancy, and socioeconomic status.<sup>12</sup>

In addition to the questionnaires to measure prenatal stress, the study included an endocrinological analysis of maternal cortisol levels in saliva. The measured cortisol levels proved to be statistically insignificant with very little difference in similar populations. Gutteling et al<sup>12</sup> concluded that cortisol levels in mothers are not linked to behavior in their offspring.<sup>12</sup>

The toddlers' behavior was measured using a temperament questionnaire, a problem list questionnaire, and an observation by trained psychologists. The temperament questionnaire was completed by parents and included 24 questions about behavior, adaptability, and attention regulation. Results of those questionnaires were compared to questionnaires completed at three months and eight months.<sup>12</sup>

The behavior problem checklist, "Problem behavior: the Child Behavior Checklist 2-3" was also completed by parents when the child was 27 months.<sup>1</sup> Lastly, attention regulation was measured using the "Bayley Scores of Infant Development 2-3" by trained psychologists who were blinded to prenatal stress.<sup>1</sup> The psychologists evaluated the toddler for developmental milestones such as object orientation, attention span, emotional tone, cooperativeness and fearfulness.<sup>12</sup>

After all data was collected a logistic regression was used to analyze the data. The information from the logistic regression allowed the researchers to account for the potential covariates and find a correlation between prenatal stress and the behavior problems of toddlers. Gutteling et al<sup>12</sup> reported that total problem behavior correlates with perceived stress during pregnancy (OR 1.17, 95% CI of 1.05 – 1.31,  $P = 0.01$ ) and



attention regulation problems correlate with the mother's fear of bearing a handicapped child (OR 1.46, 95% CI of 1.07-1.99,  $P = 0.02$ ).<sup>12</sup>

**Study 2: Attention deficit/hyperactive disorder in the offspring following prenatal bereavement: A nationwide follow-up study in Denmark, Li et al**

This very large population based cohort observational study<sup>14</sup> examined the correlation between bereaved mothers and the outcome of attention deficit/hyperactivity disorder (ADHD) in their offspring. ADHD was defined in this study as a child who received the hospital diagnosis of ADHD (ICD-10 code F90),<sup>14</sup> or children who were prescribed and filled a prescription for one of three ADHD medications: Methylphenidate, Atomoxetine, or Modafinil.<sup>14</sup>

Conducted in the years from 1991-2001, participants included in this study were pregnant mothers who experienced the death of a loved-one during pregnancy or one year prior, and their offspring. Those who were excluded from this study were children diagnosed with autism or mental retardation, low birth weight (less than 2500 grams), less than 37 weeks gestation, Apgar of less than 10 five minutes after birth or pregnancies of multiple fetuses.<sup>14</sup>

The authors, Li et al,<sup>14</sup> report a total of 29 094 of 1 015 910 children were exposed to stress of prenatal bereavement. They assumed that the death of a child or spouse would be more stressful than the bereavement of the loss of another family member and they also assumed there would be a difference in ADHD diagnosis between boys and girls. A regression model was used to determine hazard ratios to correlate ADHD and prenatal bereavement. Therefore, the authors reported their data accordingly:

of the children exposed to prenatal stress of the loss of a child or spouse, 55 had ADHD, whereas in the unexposed group, 9 982 children had ADHD (HR 1.18, 95% CI 0.91-1.54). However, 51 total boys in the exposed group (exposed to prenatal stress of bereavement of a child or spouse) had ADHD and 8 201 unexposed had ADHD (HR 1.37, 95% CI 1.03-1.79).<sup>14</sup>

Li et al<sup>14</sup> also analyzed boys with ADHD who were exposed to the prenatal stress of bereavement specifically during pregnancy as opposed to the one year prior, and found more statistically significant evidence: 11 boys with ADHD were exposed to prenatal bereavement of the death of a child or spouse (HR 2.10, 95% CI 1.16-3.80), and even more significant were the results from the exposure during the third trimester: 5 boys with ADHD were exposed to prenatal stress of bereavement of the death of a child or spouse specifically during the third trimester of pregnancy (HR 2.98, 95% CI 1.24-7.16).<sup>14</sup>

The authors clearly state that they believe that the death of a child or spouse during pregnancy produces the most severe types of psychosocial stress in mothers, therefore, only the most significant stress potentially leads to ADHD in offspring.<sup>14</sup>

### **Study 3: The links between prenatal stress and offspring development and psychopathology: disentangling environmental and inherited influences, Rice et al**

This cross-sectional analysis of *in vitro* fertilization (IVF) pregnancies<sup>15</sup> separated environment stress from genetic. The study looked at the difference in the fetuses who were related to the mother compared to fetuses who were unrelated to the mother and the outcome of child mental health.

The subjects included in this study were children conceived through IVF between 1994 and 2002. Those children were divided into groups based on relatedness to the mother: homologous IVF, sperm donor, oocyte donor and embryo donor. Included in the study were patients of nineteen IVF clinics in the United Kingdom and one in the United States, with a total of 585 patients who gave consent. The authors reported that complete data was collected for a total of 474 subjects. Ultimately, only the United Kingdom clinic data was used because prenatal records from the United States were not available for analysis. There was no mention of those who were excluded from the study, nor was there mention of follow-up.<sup>15</sup>

The data collected for analysis consisted of prenatal questionnaires completed by mothers retrospectively regarding their perceived stress level during each stage of pregnancy, questionnaires completed by parents regarding child's behavior, and a questionnaire completed by parents regarding their child's symptoms of ADHD.<sup>15</sup>

The authors mentioned an attempt to adjust for covariates such as pregnancy complications, maternal tobacco use, child age, gender, and socioeconomic class. Several other outcomes were measured including birth-weight and gestational age, but only child mental health is relevant to this review. The category of mental health was then further divided into child antisocial behavior, child anxiety, and child ADHD.<sup>15</sup>

The key to the analysis of the data in this study was whether or not a correlation between prenatal stress and a previously mentioned measured outcome was found in the related group opposed to the unrelated group. Such a finding would indicate the

correlation was likely genetically inherited rather than caused by the stressful environment *in utero*.<sup>15</sup>

The authors reported that prenatal exposure to stress had a significant association with antisocial behavior in offspring regardless of relatedness. ( $\beta = 0.190$ ,  $P = 0.02$  unrelated,  $\beta = 0.186$ ,  $P = 0.001$  related). This study produced results that indicate that ADHD is less related to environmental stress and more likely to be related to genetics ( $\beta = 0.095$ ,  $P = 0.25$ , unrelated,  $\beta = 0.163$ ,  $P = 0.001$  related).<sup>15</sup>

## **DISCUSSION**

There is evidence to suggest that there is a link between prenatal stress and behavior issues in children. All three reviewed studies presented some level of adverse outcomes related to psychosocial stress endured during pregnancy. In addition, each study focused on the stress of psychosocial rather than physical or previously diagnosed mental illness such as anxiety and depression. Each study presented findings of varying degrees of behavior disorders from difficult temperament to ADHD to antisocial behavior. In the three studies analyzed, there does appear to be a correlation between prenatal psychosocial stress and behavior disorders in the offspring.

All three studies had limitations which were documented and accounted for and some that were not. There are three primary limitations to the first study.<sup>12</sup> First, informant bias in the questionnaires could alter the results in either direction. It is reasonable to assume that questionnaires as measures of stress could be an inaccurate measure due to the subjective nature. Stress is perceived differently by individuals and is

therefore reported differently. Regardless, questionnaires as a measure of data are subjective rather than objective.

It is unlikely that the subjects of this study are a good representation of the general population. It may be that the subjects who participated in the first study volunteered to do so because they perceived they had more stress and were concerned about it; conversely, some may have opted-out of participating in the study because they didn't feel stressed. Another factor to evaluate when attempting to generalize the conclusions of Study 1<sup>12</sup> is the fact that subjects with psychological risk factors were excluded as participants.<sup>12</sup> The NIMH estimates that in a given year 6.7% of Americans are diagnosed with major depressive disorder, 2.6% are diagnosed with bipolar disorder, and 18.1% are diagnosed with an anxiety disorder.<sup>16</sup> Any study excluding individuals with these psychological disorders would be missing a large portion of the general population.

Genetic factors were not well analyzed in Study 1.<sup>12</sup> It is possible that the children who were observed could have an inherited behavior disorder regardless of their exposure to prenatal stress. Study 3<sup>15</sup> attempted to separate environment from genetics to answer this question about nature vs. nurture.<sup>15</sup>

Finally, although well written and well presented, the authors of Study 1<sup>12</sup> were vague in presenting the exact number of children who were evaluated. The number of those studied is unclear. It is written in the abstract that "complete data were available for 103 healthy toddlers".<sup>12</sup> In the method's section, 119 is the number they present as their subjects. In Table 4 of the study, the number of subjects (N) listed for mean cortisol

levels is 103. It is up to the reader to conclude that 16 participants were lost due to missing records of cortisol measurements. The article would be more influential if the subjects and data were clearly presented.

Overall, the quality of the study is very low (Table 1). The study started as low quality because it is an observational study and it is difficult to control for potential variables. Such variables may include: The attrition rate may reflect the fact that the parents who stick with the study are motivated to participate because they think their child may have a behavior problem or perhaps the personality of the parent is that they are anxious. In addition, data could be skewed by possible reporting bias of parents who are completing questionnaires about their child's behavior. Given the fact that the study has these limitations, it was downgraded. However, the information presented in the study is important enough to be aware of a potential correlation between prenatal stress and behavior problems in children.

In the second study,<sup>14</sup> the limitation had more to do with adequately gathering data. This study does have one potentially significant limitation in that two of the medications used to treat ADHD are also used to treat narcolepsy.<sup>14</sup> Patients with other conditions for which these medications are prescribed, were not excluded from the study. Assuming all children treated with Methylphenidate or Modafinil have ADHD could potentially skew the correlation between prenatal bereavement and ADHD.

As with all observational studies, the results can have multifactorial causes. For example, in Study 2<sup>14</sup>, is the ADHD diagnosis related directly to the prenatal stress or could it be that a child is being raised by a single parent following the death of a spouse?

Given that this is a psychological question, many variables could participate in the behavior development of a child. One of these variables, for example, could be genetics which is addressed in Study 3.<sup>15</sup>

Regarding the quality of Study 2,<sup>14</sup> it received a very low GRADE but the topic is important. Because this is another observational study it begins with a low grade. It was downgraded based on the imprecision of the primary results. However, the authors did report a correlation between prenatal stress and the secondary outcome of an ADHD diagnosis specifically in boys. The numbers are precise, significant and imply a positive relationship between prenatal stress and male offspring with ADHD.

There were several additional strengths of Study 2<sup>14</sup> in regards to the methodology. For example, size of the study is very large study and the design is scientifically based; the data collected were from databases not from questionnaires. The prenatal stress of bereavement, and an ADHD diagnosis are objective data rather than subjective as might be found in studies that rely on questionnaires.

In the third study<sup>15</sup>, there are many limitations. The most important limitation with the potential for informant and recall bias is that all of the data is subjective. The study relied completely on questionnaires. First, the mothers retrospectively completed questionnaires about their stress during pregnancy. Second, these mothers and their partners completed questionnaires about their child's behavior. As mentioned in the discussion of Study 1<sup>12</sup>, there are a number of reasons parents may answer the way they do about their own children. In some cases, parents may be overly sensitive to their child's behavior whereas another parent may not be as aware of their child's problem

behavior. A better study would gather data in an objective way, like having psychological evaluations as in Study 1<sup>12</sup>.

Next, there is a potential difference in the behavior of children conceived with IVF than in those naturally conceived. Perhaps there is additional stress by IVF mothers due to the inability to naturally conceive. It is reasonable to assume that parents turn to IVF when they have been unable to conceive naturally. This could create financial burden to the parents in addition to a sense of physical failure they may feel for their inability to conceive, for example. And, perhaps the IVF treatments and preparations for the fertilization are stressful, adding a time commitment and worry if the treatments fail.

Another limitation is the wide age range of children (4-10 years) studied. The questionnaires did not account for varying stages of development and childhood behavior over those stages. Typically, a four-year-old child behaves very differently from a ten-year-old child and that four-year-old may be in a difficult “stage” at the time of the study. The child may be evaluated differently at a different developmental stage. These potential variants were not addressed in the study’s write-up.

Finally, there could potentially be postnatal variables that were not addressed which could alter the correlation between prenatal stress and behavior of offspring. For example, perhaps prenatal stress is not the predictor of a child behavior but another life change event such as a divorce or incarceration of a parent, a *postnatal* stress event that could contribute to the behavior problem.

This study is lacking validity and quality for additional reasons pertaining to the presentation of the data. There is no mention of follow-up or of attrition in the study; this



information was completely omitted in the methods and results sections. The results table is not thoroughly discussed so the numbers are ambiguous. The authors chose to statistically analyze their data using *beta* ( $\beta$ ) as a measurement, which is not as clearly understood as hazard ratios, odds ratios, or standard deviations. Finally, the results table is poorly presented with far too many variables being compared or correlated. Some explanation of the presented data would improve the quality of this study.

Another flaw in this design is the fact that there are many variables in the population studied and therefore the results cannot be generalized to the public. As previously mentioned, it is reasonable to assume that the subjects may experience more significant prenatal stress due to their method of conception, *in vitro* fertilization. In addition, perhaps IVF parents have less financial burden than the general population. IVF is a costly procedure generally not covered by insurance. Perhaps parents who can afford IVF have less financial burden over all. These variables do not translate well to the general population. For these reasons, the GRADE given to this study is very low quality of evidence.

Given the limitations of Study 3<sup>15</sup> mentioned above and the added strengths of Study 2<sup>14</sup>, this reviewer finds more validity in the correlation between bereavement and ADHD in boys presented by Li et al<sup>14</sup> than the contradictory information presented in this study by Rice et al.<sup>15</sup>

## **CONCLUSION**

The three studies reviewed indicate a correlation between prenatal stress and behavior disorders in children. Despite the fact that these observational studies are of

very low quality, the question is important and findings are compelling enough to study the subject further and change the way providers practice in clinic. A well designed study is needed to influence more clinicians to be aware of the potential outcomes of prenatal stress.

The following is a suggestion for a future study: a large, population-based, observational study in which pregnant subjects, including those individuals with mental health risks, and their offspring are gathered from the networking of various electronic medical records (EHR). Trained psychologists would gather data objectively through interviews of the pregnant subjects at each trimester, as well as the observation of child behavior at several developmental stages.

The correlation between prenatal psychosocial stress and the behavior of children is an important component potentially affecting the clinical practice of providers in obstetrics, family and pediatric clinics. Understanding the potential for risks of behavior problems in children who are exposed to prenatal stress, it is appropriate to implement screening tools and when indicated recommend stress-reducing activities, therapies and groups for pregnant mothers.

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## References

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1. Huizink AC, de Medina PG, Mulder EJ, Visser GH, Buitelaar JK. Psychological measures of prenatal stress as predictors of infant temperament. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2002;41(9):1078-85.
2. Child Behavior Disorders. MedlinePlus, National Institute of Mental Health. <http://www.nlm.nih.gov/medlineplus/childbehaviordisorders.html>. Updated April 16, 2012. Accessed August 16, 2012.
3. LaRosa, Angela. Developmental and Behavioral Screening Tests in Primary Care. Uptodate.com [http://www.uptodate.com/contents/developmental-and-behavioral-screening-tests-in-primary-care?source=search\\_result&search=childhood+behavior&selectedTitle=1~150](http://www.uptodate.com/contents/developmental-and-behavioral-screening-tests-in-primary-care?source=search_result&search=childhood+behavior&selectedTitle=1~150). Updated May 2, 2012. Accessed August 16, 2012.
4. Attention Deficit Hyperactivity Disorder. MedlinePlus, National Institute of mental Health. <http://www.nlm.nih.gov/medlineplus/attentiondeficithyperactivitydisorder.html>. Updated May 11, 2012. Accessed August 16, 2012.
5. US Department of Health and Human Services. National Institute of Mental Health [pamphlet]. *Attention Deficit Hyperactivity Disorder (ADHD)*. NIH publication No. 08-3572. Revised 2008. Available at [http://www.nimh.nih.gov/health/publications/attention-deficit-hyperactivity-disorder/adhd\\_booklet.pdf](http://www.nimh.nih.gov/health/publications/attention-deficit-hyperactivity-disorder/adhd_booklet.pdf). Last accessed August 16, 2012.
6. DiPietro J. The Role of Prenatal Maternal Stress in Child Development. *Current Directions In Psychological Science (Wiley-Blackwell)* [serial online]. April 2004;13(2):71-74. Available from: Psychology and Behavioral Sciences Collection, Ipswich, MA. Accessed August 16, 2012.
7. Dohrenwend BP. Inventorying stressful life events as risk factors for psychopathology: Toward resolution of the problem of intracategory variability. *Psychological Bulletin*. 2006;132(3):477-95.
8. Holmes, Thomas and Rahe, Richard. The Social Readjustment rating Scale. *Journal of Psychosomatic Research*. 1967;11:213-218.
9. Schneider ML, Coe CL, Lubach GR. Endocrine activation mimics the adverse effects of prenatal stress on the neuromotor development of the infant primate. *Developmental Psychobiology*. 1992;25:427-439
10. Barbazanges A, Piazza PV, Le Moal M, Maccari S. Maternal glucocorticoid secretion mediates long-term effects of prenatal stress. *The Journal of Neuroscience*. 1996;16(12):3943-3949. <http://www.jneurosci.org/content/16/12/3943.full>. Accessed August 24, 2012.

11. Weinstock, M. Does prenatal stress impair coping and regulation of hypothalamic-pituitary-adrenal axis? *Neuroscience and Biobehavioral Reviews*. 1997;21(1):1–10
12. Gutteling BM, de Weerth C, Willemsen-Swinkels SH, et al. The effects of prenatal stress on temperament and problem behavior of 27-month-old toddlers. *European Child and Adolescent Psychiatry*. 2005;14(1):41-51.
13. Cohen, Sheldon, Kamarck, Tom, Mermelstein, Robin. A Global Measure of Perceived Stress. *Journal of Health and Social Behavior*. 1983; 24(4):385-396 <http://www.jstor.org/stable/2136404>. Accessed August 24, 2012.
14. Li J, Olsen J, Vestergaard M, Obel C. Attention-deficit/hyperactivity disorder in the offspring following prenatal maternal bereavement: a nationwide follow-up study in Denmark. *European Child & Adolescent Psychiatry*. October 2010;19(10):747-753. Accessed August 16, 2012.
15. Rice F, Harold G.T., Boivin J, van den Bree M, Hay D.F. and Thapar A. The links between prenatal stress and offspring development and psychopathology: disentangling environmental and inherited influences. *Psychological Medicine*. 2010;40(2):335-345.
16. The Numbers Count: mental Disorders in America. National Institute of Mental Health. <http://www.nimh.nih.gov/health/publications/the-numbers-count-mental-disorders-in-america/index.shtml>. Reviewed September 12, 2012. Date Accessed September 13, 2012.

**Table I: Characteristics of Reviewed Studies**

|                                     |   |                        | Downgrade Criteria  |                         |  |                            |                                  |                            |          |            |
|-------------------------------------|---|------------------------|---|-------------------------|--|----------------------------|----------------------------------|----------------------------|----------|------------|
| Studies                             | Design  | Outcome                | Limitations   | Indirectness            | Imprecision  | Inconsistency              | Bias                             | Result                     | Quality  | Importance |
| <b>Gutteling et al<sup>12</sup></b> | Observational:<br>Ongoing prospective longitudinal                            | Total problem behavior | Serious limitations:<br>Selection and informant bias likely | No serious indirectness | No serious imprecision                               | No serious inconsistencies | Informant bias likely            | Odds Ratio (95% CI)        | Very Low | Important  |
|                                     |   |                        |   |                         |  |                            |                                  | 1.17 (1.05 - 1.31)         |          |            |
| <b>Li et al<sup>14</sup></b>        | Observational:<br>Nationwide population-based cohort study                    | ADHD                   | No serious limitations                                      | No serious indirectness | Serious imprecision:<br>confidence intervals cross 1 | No serious inconsistencies | No bias likely                   | Hazard Ratio (95% CI)      | Very Low | Important  |
|                                     |   |                        |   |                         |  |                            |                                  | 1.18 (0.91- 1.54)          |          |            |
| <b>Rice et al<sup>15</sup></b>      | Observational:<br>Cross-sectional analysis of prenatal cross-fostering design | Antisocial behavior    | Limitations:<br>Incomplete follow-up                        | No serious indirectness | No serious imprecision                               | No serious inconsistencies | Recall and informant bias likely | Beta                       | Very Low | Important  |
|                                     |   | ADHD                   |   |                         |  |                            |                                  | Antisocial behavior: 0.190 |          |            |
|                                     |   |                        |   |                         |  |                            |                                  | ADHD: 0.095                |          |            |