Prenatal and Postnatal Contributors to Development in Infancy

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Project Summary.

There is increasing evidence that the prenatal environment sets certain aspects of infant cognitive and emotional development during the first months and years of life. This idea has been labelled the "Foetal Programming Hypothesis" (FPH) and researchers who have studied it have shown how specific factors related to maternal stress and the consumption of alcohol, tobacco and drugs during the prenatal period, are related to cognitive, emotional and psychophysiological markers of infant development and functioning (Huijbregts, Séguin, Zoccolillo, Boivin, & Tremblay, 2008; Huizink & Mulder, 2006; Weinberg, Sliwowska, Lan, & Hellemans, 2008; Weinstock, 2008). Maternal stress is also related to increased levels of physiological markers of stress (such as cortisol) which easily crosses the placental barrier, as do alcohol and substances in drug and tobacco products. Such substances have been shown to influence brain development in animal research in regions related to memory and emotional development (Gunnar & Fisher, 2006; Weinberg et al., 2008).

Different prevention strategies have been applied to reduce the levels of these prenatal variables, especially in high-risk populations. The results of these initiatives has been unclear and leave three questions unaddressed: First, few prevention strategies have been assessed in designs where mothers have been randomly assigned to different intervention conditions and where the effects of the intervention is shown to be superior to the community and hospital-based services that high-risk expecting mothers receive. This is an important issue because it has been shown that even high-risk expecting mothers spontaneously lower their consumption of problematic substances. Second, not all studies show expected effects on stress and consumption, and when effects are found, they are rarely correlated to infant developmental outcome. Third, when infant outcome has been assessed, critical postnatal factors known to influence development have often been ignored, such as mother-infant interaction and family conflict. Thus, while foetal programming appears to be an important target of prevention, critical studies involving randomized designs and consideration of postnatal factors are lacking. Such experimental studies promise not only to help practitioners be more effective with high-risk mothers, but also provide the opportunity to more clearly estimate the importance of foetal programming because prenatal variables are manipulated and postnatal variables co-varied.

Presently, 76 moderate to high risk young mothers (<24 years old; not more than one year of post-secondary education) were randomly assigned to a control or an intervention group. Assessments were made when they were between 16 and 22 weeks pregnant, and 3 months after birth. Variables assessed covered the period between the first and second assessment. The control group was exposed to hospital and community-based care for moderate and high risk mothers. The intervention group received the same care, plus 6 home-visits specifically focused on maternal stress, and tobacco, alcohol and drug consumption. Assessments were made of proximal prenatal variables (stress, consumption), confounding postnatal variables (mother-infant interaction, marital adjustment, daycare experience), outcome postnatal variables (stress, consumption) and infant developmental outcome variables (cognitive and socio-emotional development). Data were analyzed through hierarchical multiple regression strategy. We hypothesized that: 1) intervention will prove effective in reducing prenatal maternal stress, and tobacco, alcohol and drug consumption after comparison with the control group; 2) Changes in prenatal variables and postnatal factors, will contribute to infant

developmental outcome; 3) Changes will remain after controlling for the quality of mother-infant interaction, family conflict and infant daycare experience.

Results show that, contrary to expectations, the intervention proved ineffective in changing maternal levels of prenatal stress or consumption. As such, evidence for foetal programming could not be explained using the experimental design that was proposed. Consequently, the programming hypothesis was examined by way of hierarchical regression analyses. Here, evidence for foetal programming was observed. Specifically, prenatal levels of alcohol consumption were linked to infant salivary cortisol concentrations, and prenatal maternal anxiety was associated to infant cognitive and emotional development. There was marginal support for a relation between major life events (an indicator of stress) and infant emotional development and maternal smoking and infant cortisol concentrations. Postnatal levels of maternal interactive sensitivity, marital adjustment and daycare experience were unrelated to infant cognitive or emotional outcomes, indicating that at the time infant outcome measures were taken, prenatal factors weighed more heavily in predicting infant outcome.

Project Description

a. Objectives of the research: The primary objective of this study was to examine the effectiveness of a prenatal prevention strategy intended to reduce maternal stress and the use of alcohol, tobacco and drugs by young moderate to high risk mothers. Using an experimental design with an intervention and control group has clear practical objectives, but also serves to estimate foetal programming effects. The study involves a randomized design. Proximal outcome measures are maternal stress and consumption of alcohol, tobacco and drugs. Covariates include postnatal levels of prenatal variables (stress, consumption), mother-infant interaction, family conflict and infant daycare experience. Distal outcome measures are infant cognitive and socio-emotional development.

b. Rationale and background literature. There is increasing evidence that the prenatal environment sets certain conditions related to infant socio-emotional and cognitive development and learning during the first months and years of life. Research on the “Foetal Programming Hypothesis” (FPH) has come from both animal (rodents; non-human primates) and human studies. The FPH refers to the notion that biological systems, such as the foetus, adapt to environmental input, but that once this adaptation has taken place, usually over a certain period of time and at sensitive periods during pregnancy, adaptation is no longer possible. After birth, the human infant’s ability to adapt is remarkable (Gunnar & Fisher, 2006), however, in the context of overexposure to maternal stress-related glucocorticoids (e.g., cortisol) that cross the placental barrier, and overexposure to tobacco, alcohol or drugs, the system has changed to the degree that it becomes somewhat maladapted in the postnatal environment (Bergman, Sarkar, O’Connor, Modi, & Glover, 2007; Keenan, Sheffield, & Boeldt, 2007; O’Connor, 2003).

Empirical support for the FPH come from highly controlled studies with animals and longitudinal, correlational research with humans. Animal studies demonstrate that exposure to different substances predispose offspring to a number of syndromes that may compromise later cognitive and socio-emotional development. Maternal prenatal stress experience also appears to have a determining impact, as foetuses exposed to elevated levels of maternal cortisol show lower levels of hippocampal plasticity and lower functioning working and long term memory. This experimental research is convincing and suggests high validity for the hypothesis that foetal exposure to elevated levels of toxic substances may permanently modify basic physiology (Bertram & Hanson, 2002; Levine, 2005; Weinstock, 2008).

Human research has been conducted in correlational, longitudinal studies. Maternal stress and exposure to toxic substances has been shown to be related to later indices of learning (Huizink & Mulder, 2006) and different aspects of emotional regulation and social development across development (Gunnar & Fisher, 2006; Gutteling, de Weerth, Zandbelt, Mulder, Visser, & Buitelaar, 2006; Mennes, Van den Bergh, Lagae, & Stiers, 2009; Van den Bergh, Mulder, Mennes, & Glover, 2005). In a recent review of 14 studies testing the FPH in relation to the impact of maternal stress, Van den Bergh and colleagues have demonstrated that in general, there appears to be a robust association between stress and different indices of child development, with effects being documented in some studies up until adolescence (Mennes et al., 2009). Similar findings have been found regarding the impact of alcohol, tobacco and drugs on the developing foetus (Huizink & Mulder, 2006; Mokdad, Brewer, Naimi, & Warner, 2007). Coherent with the FPH, these correlational studies suggest that the prenatal environment is one of the major mediators of the relation between the child's ecology and development.

Researchers have emphasized the importance of such findings for promoting comprehensive prenatal prevention programs with parents who are at greater risk for being exposed to stress, alcohol, drugs or tobacco (Olds, 2007; Olds, Saddler, & Kitzman, 2007). Prevention research has been important because both researchers and practitioners wish for the most optimal conditions for health child development and in this respect, the development and validation of prevention strategies is a critical public health concern. Furthermore, well conducted evaluations allow researchers to test the validity of basic hypotheses. In this context, validation studies of prenatal prevention programs allow us to critically examine the validity of the FPH in a way that correlational studies do not allow.

The purpose of this study was two-fold. First, our group has been involved in the development and validation of prevention strategies intended for high risk populations since 1998 (Moss, Cyr, Dubois-Comtois, Tarabulsy, St-Laurent, & Bernier, under review; Tarabulsy, Pascuzzo, Moss, St-Laurent, Bernier, Cyr, & Dubois-Comtois, 2008) and we are currently elaborating an approach to prenatal prevention with primiparous moderate to high risk mothers to improve infant developmental outcome. A first goal of this study is to validate this approach. Second, we hoped to use this study to address some unresolved issues regarding the FPH. These issues emanate from the longitudinal studies that have been used to address the FPH in humans, as well as from evaluations of prenatal prevention strategies.

<u>Problems with the FPH.</u> Events that take place during the prenatal period have the potential of permanently altering infant development. Foetal alcohol syndrome is a dramatic example of this reality. Our point is not to undermine this basic idea. Rather, we wish to address the possibility that it is difficult to tease out the effects of prenatal programming from other important effects, especially those that are known to influence infant developmental outcome that occur during the postnatal period. We point to four basic characteristics of FPH and prevention research.

1. Elevated maternal stress, smoking and drug/alcohol use in the prenatal period are highly correlated with the levels of these variables during the postnatal period (Morasco, Dornelas, Fischer, Oncken, & Lando, 2006) and with the quality of mother-infant interaction and other aspects of the postnatal environment known to influence infant developmental outcome (Gunnar & Fisher, 2006; Levine, 2005). Thus, it is noteworthy that studies of the FPH have rarely accounted for postnatal levels of prenatal variables. Several studies have shown that levels of maternal stress, tobacco, alcohol and drugs may actually increase after birth and be communicated to infants through breast feeding (Lawrence & Haslam, 2007) Furthermore, FPH studies have rarely included appropriate assessments of mother-infant interaction, parental conflict and other variables known to be associated to infant development (Gunnar & Fisher, 2006; Lemelin, Tarabulsy, & Provost, 2006). This methodological problem has been observed in many studies relating infant development to maternal stress, smoking, and drug/alcohol use (Jacobson, Bihun, & Chihoto, 1999; Mennes et al., 2009; Steinhausen, Del Mas, Lederman, & Metzke, 2006; Van den Bergh et al., 2005; Waskschlag, 2006). To appropriately tease out the effect of foetal programming on development, it is critical that researchers include postnatal assessments of prenatal variables and quality measures of postnatal child experience.

2. High quality evaluations of the impact of prenatal intervention may compensate for such methodological issues. However, most prenatal prevention programs remain unevaluated (Moos, 2006) and most of those that are use pre-experimental or quasi-experimental designs, which are known to have lower internal validity. This is particularly problematic because of spontaneous reductions in maternal use of toxic substances by expecting women when they realize that they are pregnant (Morasco et al., 2006). Thus, part of the reductions in the use of toxic substances may be attributable to spontaneous changes in maternal habits. Researchers have suggested that in the absence of randomized control groups, prevention results probably overestimate program effectiveness (Albrecht et al., 2006).

3. Randomized designs have the potential to reveal information about developmental process that originates during the prenatal period because of the manipulation of basic prenatal variables (Levine, 2005). However, evaluations of prevention strategies often focus exclusively on immediate post-intervention measures of maternal prenatal factors to show effectiveness (Albrecht et al., 2006). While these reports show that it is possible, with brief, structured intervention to reduce levels of toxic substances and maternal stress at the end of the prenatal period or shortly after the birth of the infant, few studies have actually included assessments of infant cognitive or socio-emotional development.

4. Some studies have used randomized trials and have measured infant outcome. Perhaps the most solid demonstrations have been those by Olds, who has shown the effectiveness of a broad prevention strategy in three large scale trials focusing on the prenatal period and continuing until the infant is two-years-old (Olds, 2007; Olds et al., 2007). These strategies clearly show effects in infant cognitive and socio-emotional development during the postnatal period. With respect to the FPH, however, these approaches do not provide information regarding the manner in which changes during the prenatal period affect infant and child development because intervention continues between birth and the first child assessments. It is unclear that changes are due to prenatal changes or postnatal changes in parenting and home environment. While these findings are encouraging for clinicians, they do not help understand how prenatal changes relate to infant outcome.

Presently, we propose to evaluate in a randomized design an intervention strategy that has as its primary objective changes in prenatal maternal stress, smoking and alcohol/drug use, and we wish to examine how changes in these prenatal variables influence early indices of cognitive and socio-emotional development in young infants. Critical postnatal variables will also be measured: maternal stress, smoking, alcohol/drug use, as well as mother-infant interaction, family conflict and use of non-maternal care to examine contributors to infant cognitive and socio-emotional development when infants are aged 3 months. We make the following hypotheses:

1. As in other research, we will show that a short, 6-meeting prevention strategy is effective in reducing levels of maternal stress, smoking and alcohol/drug use during the prenatal period.

2. We expect that changes in prenatal levels of stress, smoking and alcohol/drug use will be linked to infant cognitive and socio-emotional developmental outcome.

3. We will examine the same questions but will control for the quality of mother-infant interaction, family conflict and infant daycare experience. We expect that significant associations will be observed between variables assessed pre and postnatally and that contributions to infant development will come from prenatal, intervention and postnatal variables.

Method

Recruitment and participants: This study was nested within a larger program conducted by Tarabulsy and funded by the SSHRC and the FQRSC (Quebec). Recruitment took place at the Centre Hospitalier Universitaire de Québec, Pavillon St-François d'Assise (CHUQPSA) in Québec City. Expecting mothers aged 24 years or less were recruited by nurses at their first medical visit (12-14 weeks of pregnancy) or at the first compulsory ultrasound (22 weeks). This hospital sees the majority of high-risk pregnancies in the Quebec area. Recruitment took place between December 2007 and September 2008. Recruitment for the Tarabulsy research program is nested within the CIHR-funded "Healthy pregnancies" project headed by J. C. Forest of CHUQPSA in which all expecting mothers are interviewed. Maternal age was used as a gross index of maternal risk. Young motherhood is a well documented risk factor for greater levels of prenatal maternal stress, smoking and consumption of alcohol and drugs (Olds et al., 2007; Wakschlag, 2006). While this group is not a high-risk group, it includes a number of high-risk mothers and families. This group is chosen because it will provide sufficient variance in levels of prenatal variables to allow for the examination of the study's hypotheses, while allowing for some flexibility in recruiting procedure, ensuring that a sufficient number of expectant mothers participate within the study's time limitations. Further, the project has the objective of providing continued validation of the intervention strategy we have worked with, intended for moderate to high risk families in the social services network.

Randomization: Once recruited, subjects were randomized to the intervention and control conditions through a restricted random assignment with matching procedure (RASM).

Subjects were matched for maternal age (<20; >20) and education (finished/not finished high school). For example, if an expecting mother less than 20 years old with a high school degree is recruited, we waited for a similar mother to be recruited prior to assignment, thus generating two equal sized groups, similar on the basis of key maternal characteristics. Randomization was conducted after mothers agreed to take part in the study, after the first home visit (T1).

Table 1. Summary of Randomized trial.

Groups	T1 Prenatal 14-22 weeks pregnancy	14-22 weeks to infant birth	T2 Birth	T3 infant 3-months-old
Intervention n=38 prior to attrition	• Assessment of maternal stress, smoking, alcohol and drug use *Restricted random assignment takes place after T1, prior to application of 6 home visits.*	• Regular community services • 6 intervention home visits	**Both groups** Medical records: Perinatal Complications • Infant health and birth characteristics • Continued tracking of use of community services	**Both groups** • Assessment of maternal stress, smoking, alcohol and drug use • Assessment of quality of mother-infant interaction, family conflict, daycare experience. • Infant development • Continued tracking of use of community services.
Control n=38 prior to attrition	• Assessment of maternal stress, smoking, alcohol and drug use	• Regular community services		

Inclusion/exclusion criteria.

Inclusion criteria for mothers: Mothers were primiparous, expected a single infant (no twins were born in this study), were aged 24 years or less at recruitment and had less than one year of postsecondary education. Mothers also had to be native French-language speakers.

Exclusion criteria for mothers: Mothers expecting to leave the Quebec area within the next 12 months.

Inclusion criteria for infants: Infants were included if they were part of a singleton birth, and the mother's first infant.

Exclusion criteria for infants: The only exclusion criteria was the presence of major or lethal congenital anomalies. No infants were excluded due to this criteria.

Description of prenatal intervention. Intervention was delivered by 4 masters-level clinical psychology graduate students. The 6-home-visit, manualized strategy is made up of two components. First, we address the issue of maternal stress by providing instrumental and emotional support in family organization and preparation for the birth of the infant. This preparation takes several forms: Encouraging mothers to enrol in local prenatal courses; pointing needy mothers to community resources; helping mothers look for appropriate child care and taking a proactive role in helping them have in their home the materials necessary for the arrival of the infant. The support we provide is directed towards the specific needs that young mothers experience. This dimension of the program is inspired from research which has repeatedly shown that much of the prenatal stress that high-risk mothers experience come from not knowing what to expect from parenthood, not having appropriate support networks to help them meet the challenges of parenthood and being not familiar with community resources (Whitman, Borkowski, Keogh, & Weed, 2001). Second, with all mothers, we systematically address the issues of smoking, alcohol/drug use. Each topic is examined in four steps coherent with guidelines provided by the American Cancer Society and others (Albrecht et al., 2006; American Cancer Society, 2001; Grant, Ernst, Streissguth, & Stark, 2005; Olds et al., 2007).

1. We probe the issue of consumption to see if there is a use problem.
2. If there is a problem, we inquire to see if there is a desire to quit/reduce consumption.
3. If not, we present prepared materials to help underline the negative effects of consumption of toxic substances on foetus and positive effects of quitting; we emphasize the importance of exposing the unborn child to positive prenatal care and that mother may take steps to achieve this. We verify with the mother the possibility of setting goals that she can reach in the short term.
4. If a desire to quit or reduce use is noted, we work with the mother to set goals that may be achieved and discuss with her whether there are practical methods we can use to help her achieve these goals (Chang, McNamara, Orav, & Wilkins-Haug, 2006; Grant et al., 2005). We examine with the mother the circumstances in which she smokes/drinks/uses drugs and uses the supporting relationship we have established with her to establish an "Integrity Contract". This contract, signed by clinician and mother, stipulates ways to avoid situations where mothers are more likely to smoke/drink/use drugs and determines alternative behaviors, help seeking strategies, and other methods to help the mother have access to supportive figures. The mother is encouraged, but not obligated, to include her partner/spouse in the process. The contract further establishes steps that will be taken to work toward achieving consumption reduction goals.

In the current study, there were no mothers who identified themselves as having problems in smoking or in the use of drugs or alcohol, even though there was variation and all mothers who smoked or used drugs or alcohol reported having lowered their consumption by the time we interviewed them during their pregnancy.

<u>Structure of Intervention Home Visits.</u> Each of the 6 home visits is similar in structure. Each meeting lasts approximately 75 minutes and involves a 15 minute unstructured discussion, a 20 minute review of previous discussions and a 40 minute discussion of a new aspect of the intervention strategy. In the first meeting, time is taken for the clinician and young mother to become acquainted. Intervention materials and a manual have been prepared to guide clinicians and mothers through the program (Tarabulsy & Bussières, 2007). The first two meetings help clinicians learn of the young mothers strengths, weaknesses, assess her support base and understand her vulnerabilities to stress, smoking, alcohol and drug use. During the second meeting, we specifically address the issues of family organization, preparation for daycare (requires early registration in Québec), address issues of support and resources and begin to think about the postnatal period. These issues are followed up on in visits 3-5. In addition, visits 3-5 focus on nutrition, smoking, alcohol and drug use. If the mother does not have needs with regard to these issues, we present the information without a contract. Visit 6 allows the young mother to ask any unaddressed questions and to touch base on all issues that have been examined and to address questions related to birth and the postnatal period.

<u>Measures.</u>

<u>Maternal stress:</u> Prenatal maternal stress was assessed examining three dimensions of stress: Life events were measured with the Life Events Scale of the Parental Stress Index (Abidin,

1995), maternal anxiety were assessed with anxiety items from the Symptoms Checklist – Revised (Derogatis, 1994) and stress experience was measured with the Psychological Stress Measure (Lemyre, & Tessier, 1988).

Smoking, Alcohol and Drug use: Information relative to these variables were obtained with the questions from the Québec Longitudinal Study of Child Development (QLSCD). This self-report information eventually allows us to compare reported rates of consumption with that of a provincially representative sample of new mothers.

Mothers answer two questions. The first determines whether they smoke, drink or use drugs or not. The second establishes the frequency of the use of these substances. For smoking, the number of cigarettes smoked per day is provided. For alcohol use, a 7 point Likert scale item is answered where a score of 1 corresponds to one drink per month or less, and a score of 7 corresponds to daily consumption. For drug use, we ask that mothers tell us how many times they have used drugs, and what types of drugs, since the beginning of their pregnancy.

This information was collected at T1 and T3. At T1, mothers provide information regarding smoking and alcohol and drug use since the beginning of their pregnancy. At T3, they provide information regarding the period between T1 and infant birth.

Quality of mother-infant interaction: The quality of mother-infant interaction was assessed at the 3-month postnatal visit with the Pederson and Moran Maternal Behavior Q-Sort (MBQS; Pederson & Moran, 1996). This is a 90-item instrument where each item describes potential maternal interactive behaviors. Following the 120 minute home visit, items are sorted, based on the Q-Sort method, as a function of observations. Scores may range from -1.0 to 1.0. This is one of the more valid and reliable observation schemes for mother-infant interaction (Lemelin et al., 2006; Tarabulsy et al., 2005). The MBQS was completed following the visit. Inter-rater reliability was established for a subset of 25 dyads (37.31%) and was found to be .81 ($p<.0001$).

Family conflict: Dyadic conflict is perhaps the most important family-based stressor related to quality of caregiving and is experienced by the infant by way of interactions but also directly, without mediation (Abidin, 1995). At first, we intended to assess this construct with the Conflict Tactic Scale (CTS; Straus et al., 1996), which has been used in a number of large scale investigations of family violence. However, after a few parents deemed the questions to be overly intrusive, we decided to change the scale and use the Dyadic Adjustment Scale (Spanier, 1976), which pertains more specifically to the overall quality of the relationship the mother has with her partner. While this is a more focused measure, it was selected because it is widely used and possesses sound psychometric characteristics. Cronbach’s alpha in the present study was .93.

Daycare experience: In high-risk circumstances, exposure to high-quality non-family based care, such as daycare, has been shown to be linked to improved development (Côté et al., 2007). At the 3 month postnatal assessment, we asked a number of questions concerning daycare experience, many drawn from the QLSCD, to address this question. Specifically, we questioned whether mothers make regular use of non-family child care and the number of hours per week that infants are exposed to non-family care.

Infant Cognitive Development: T3 cognitive development was assessed via the Bayley Scales of Infant Development (Bayley, 1993), the most widely used assessment of early cognitive development. Our lab has had many positive psychometric experiences with this assessment (Lemelin et al., 2006). Presently, research assistants were trained to 95% reliability with an expert clinical psychologist who has administered several hundred Bayley Scales prior to conducting assessments and providing training in the current study.

Infant Emotional Development: 3-month emotional development will be derived from two assessments that have been used to address the FPH in previous research with 3-month-old infants: Diurnal changes in salivary cortisol concentration and infant attention/arousal.

Diurnal infant cortisol secretion: Researchers have suggested that one of the mechanisms by which foetal programming operates is reflected in the diurnal rhythms of the Hypothalamus-Pituitary-Adrenocortical Axis (HPA axis; O'Connor, 2003; Van den Bergh et al., 2005). Cortisol activity follows a circadian rhythm, which is under the influence of both prenatal and postnatal events and is related to emotional regulation (Gunnar & Fisher, 2006). It is easily accessible in infant saliva. Originally, we had hoped that mothers would be able to provide us with saliva samples from their infants. However, we discovered early on in the study that some mothers objected to being asked to conduct these procedures without appropriate supervision or the presence of research assistants. To compensate for this problem, mothers were asked to extract saliva by way of a test tube and suction pump in presence of home visitors. Mothers would insert the tube in the infant's mouth and activate the electric suction pump. Saliva would then flow from the infant's mouth, through the tube into a test tube. Tubes were kept frozen at -20 degrees until they were assayed at CHUQPSA. Mothers extracted saliva upon the arrival of home visitors and just prior to their departure, approximately 120 minutes later. Research assistants asked mothers a number of questions regarding sleep, eating, illnesses and other events that may have influenced or otherwise interfered with assessments of salivary cortisol concentrations. Saliva was assayed in the Biochemistry service of the CHUQPSA with the HS enzyme-linked immuno assay synelisa sensitive procedure (ELISA).

There are two scores that will be considered in analyses regarding cortisol secretion. The first concerns absolute levels of cortisol during the home visit, indexed by the mean score of the first and second assessments. The second is the difference in the first and second assessments after the 120 minute home visit. This difference reflects the manner in which infants respond to the demands of the home visit (Gunnar & Fisher, 2006; Weinstock, 2008; Jacobson et al., 1999).

Infant attention: Early indices of infant attention have been shown to be correlated to different aspects of later socio-emotional development, such as the quality of collaborative problem-solving and peer relations, as well as attachment security (Rothbart & Posner, 2007) They have also been shown to be related to tests of the FPH, where links with maternal prenatal stress and drug use have been documented (Weinstock, 2008). Currently, infant attention was assessed with the Attention subscale of the Behavior Rating Scale of the Bayley Scales, regularly used in such contexts. Research assistants were trained to 95% reliability on the Behavior Scales with an expert clinician who has administered several hundred assessments with the Bayley Scales prior to conducting research assessments.

Procedure: Recruiting nurses obtained the coordinates from all mothers who were eligible for participation and who showed an interest for the study. They then communicated these coordinates to the research team. The research coordinator contacted the parent and set a date for T1 home visit evaluation. After T1 assessment, participants were assigned to either of the two experimental conditions using the restricted random assignment with matching procedure described above. The intervention group receives 6 intervention visits, one every 3 weeks. Telephone contact was maintained with all mothers every month. After birth, medical files are consulted to obtain information relative to infant and maternal health (T2). After two months, mothers were contacted via telephone to set a date for the T3 home visit during which developmental outcome information was obtained. All assessment meetings were conducted by trained graduate research assistants. Parents were compensated 20$ for each evaluation visit and 10$ for each intervention visit.

Participants and attrition.

In total, 124 mothers matching inclusion criteria were given information regarding the study. Ninety-four (76%) mothers agreed to receive a telephone call from research personnel. Of these 94, 76 (81%) agreed to begin participation in the study by receiving home visitors during their pregnancy. Randomization took place after this T1 visit.

The intervention and control groups were thus made up of 38 expectant mothers in each group. Table 2 presents basic participant characteristics for both groups. T-tests revealed no differences between the two groups on any of these variables.

By T3, several mothers had opted out of the study, 2 from the intervention group and 7 from the control group. Participants who remained did not distinguish themselves from participants who left the study. Analyses focused on these 67 subjects.

Mothers in the intervention group received no less than 5 of the 6 prescribed intervention visits and 28 of the 36 (77.78%) received all 6.

Different procedural problems prevented us from obtaining valid saliva samples from all of the infants. In some cases, infants were sleeping, or interrupted home visits with naps, thereby interfering with sample validity (n=14). Sometimes, mothers disagreed with the procedure and did not consent to extracting saliva (n=4), infants were overly fussy (n=4), insufficient amounts of saliva were obtained (n=5) or test tubes were inappropriately labelled by research assistants (n=6). Thus, in the specific case of analyses of saliva cortisol concentrations, analyses focused on 34 infants.

Results

Analyses proceeded in four distinct steps. First, T-tests and chi-square analyses were conducted to determine whether intervention and control groups differed on pre-intervention levels of critical variables. Whatever differences were found were covaried in subsequent analyses. Second, bivariate correlations between pre-intervention and developmental outcome variables were conducted to test whether there was evidence of foetal programming. Third, a hierarchical regression strategy was used to determine the effectiveness of the intervention on proximal variables (maternal stress, smoking, drug and alcohol use) and on infant developmental outcome. Fourth, should there be evidence of foetal programming and intervention effectiveness, hierarchical regressions will be carried out to determine whether effects remain once postnatal characteristics are accounted for.

Add the description about socioeconomic and demographic information presented in Table 1, (which should be Table 2).

1. Preliminary analyses.

Preliminary, descriptive data are shown in Table 3. Table 3 shows that intervention group mothers used alcohol less frequently than control group mothers prior to the beginning of the intervention, although the percentage of mothers reporting alcohol use was not different. Moreover, a marginal tendency was observed for control group mothers to report smoking during their pregnancy more often than intervention group mothers, prior to the beginning of the intervention. Finally drug use appeared to be more important for mothers in the control group, although none of the means approached significance and in both groups, drug use was very low.

2. Bivariate correlations.

Correlations were conducted between indicators of maternal stress (stress, anxiety, life events), smoking, alcohol and drug use and infant developmental variables (Bayley mental developmental index, attention scale, cortisol secretion). These are presented in Table 4. Table 4 reveals some evidence of associations between maternal indices of prenatal anxiety and infant cognitive development and attention at 3 months, as well as associations between prenatal alcohol consumption and both indices of infant 3 month cortisol secretion. Moreover, marginal tendencies were observed between major life events and infant attention, as well as between maternal prenatal smoking and mean levels of cortisol secretion.

Several expected associations were not found, notably between maternal stress and developmental outcome. Further, no relations were found linking drug use to developmental outcome, although this may be attributable to the very low frequency of drug use during the prenatal period in the current sample.

3. Test of intervention.

Hierarchical regressions were conducted to test for the effectiveness of the intervention strategy following the intervention, prior to the birth of the infant (as reported by mothers at T3). Regressions were conducted in the following manner:

Post-intervention dependent variable=pre-intervention dependent variable + intervention (0,1)

Analyses were conducted on all pre-intervention variables: maternal stress, maternal anxiety, life events, and indices of smoking, alcohol and drug use. Moreover, where appropriate, we controlled for levels of alcohol use frequency scores and smoking (yes/no). The purpose of these analyses was to examine whether the intervention strategy was effective in changing the levels of these pre-intervention variables.

In all analyses, the intervention did not add to the prediction of the post-intervention levels of variables. We can conclude safely that this intervention strategy was <u>not effective</u> in changing prenatal levels of maternal stress and anxiety, and use of tobacco, drugs and alcohol.

A similar set of analyses was conducted with reference to infant developmental outcome. Here the regression strategy was the following:

Developmental variable=pre intervention variable + intervention.

Again, where appropriate, we controlled for levels of alcohol use frequency scores and smoking (yes/no) as these tended to be linked to outcome variables and related to group. Analyses conducted for salivary cortisol concentrations also controlled for the time when samples were taken.

The analyses revealed that with regard to indices of cognitive development and secretion of cortisol, the intervention had no effect.

A marginally significant effect for the intervention was found for the Bayley Behavior Scale of Attention ($F(3,65)=2,63$, $p<.06$) with a significant univariate effect for intervention ($t(1)=2.75$, beta=.35, $p<.01$). Mean score for infants in the intervention group was 37.89 (se=.64). Mean score for infants in the control group was 35.25 (se=.68) (means adjusted for alcohol use and smoking). This was the only intervention effect that was documented.

4. Postnatal levels of variables, maternal sensitivity, child care experience and dyadic adjustment.

In light of current findings, it was difficult to continue to carry forward the intervention-based experimental design in further analyses. While there is some evidence of foetal programming, the intervention does not appear to have an impact on the prenatal variables involved in foetal programming. Moreover, the intervention appears to have an impact only on one of the four developmental variables considered, infant capacity for attention during the developmental assessment. Thus, it is not possible to illustrate potential causal mechanisms between prenatal factors and postnatal developmental variables with the current results. As such, there is no pertinence in conducting the final set of analyses.

The decision is made to continue to examine the basic hypothesis of the current study within a correlational design. Recall the basic question: What is the relative contribution of prenatal variables and postnatal variables in predicting infant development. In this context, we will isolate the pre-intervention variables that were related or marginally related to infant developmental outcome variables and examine whether observed relations remain when postnatal variables are considered. These variables are: maternal anxiety as it relates to infant cognitive development and attention, major life events as they relate to infant attention, smoking as it relates to infant change in cortisol concentration, and frequency of alcohol use, as it relates to both mean levels of cortisol and change in salivary cortisol concentration. In the case of attention, the only maternal or child variable that appears to be influenced by the intervention strategy, the additional variable of exposure to intervention will be added.

Table 3 presents means for maternal sensitivity and dyadic adjustment when infants were 3-months-old. It is noteworthy that neither maternal sensitivity or dyadic adjustment were related to intervention, because neither was targeted by the intervention strategy. Information regarding daycare was not pertinent to analyse. None of the 67 participating mothers used daycare in any systematic manner when their infants were 3-months-old. All made use of parents or friends as occasional “sitters”. The Province of Quebec has a policy of permitting maternity leave for all mothers during the first year of the infant’s life. All mothers in this study either benefited from this leave or were otherwise at home caring for their infant. Thus, it was not possible to investigate the possible impact of daycare experience at this stage of the study.

Hierarchical regression analyses were conducted in the following manner:

Developmental variable=post-natal variables + pre-intervention variable.

Variables were tested separately in individual regressions. In the case of cortisol variables as dependent variables, time of saliva sampling was also factored into the regression.

The associations between maternal prenatal anxiety and infant cognitive development and attention at 3-months remained even when controlling for maternal sensitivity and marital adjustment and post-natal levels of anxiety. In the case of both developmental outcomes, post-natal variables did not contribute to variance, whereas univariate effects for prenatal maternal anxiety remained significant. In fact, as Tables 5 and 6 show, the beta values are barely different from the Pearson correlations in Table 4, indicating that the postnatal variables that were examined had very little contribution to infant developmental outcome.

The marginal association between major life events and infant attention remained after controlling for maternal sensitivity and marital adjustment and post-natal life events, as shown in Table 7.

Table 8 shows the results for the hierarchical regression examining the relative contributions of prenatal and post-natal smoking, maternal sensitivity and marital adjustment to change in cortisol secretion. Results show that prenatal smoking continues to be marginally, inversely related to change in salivary cortisol concentration.

Tables 9 and 10 demonstrate that after controlling for maternal interactive sensitivity and marital adjustment and post-natal frequency of alcohol use, the frequency of alcohol use continues to significantly predict both mean level of salivary cortisol concentration and change in salivary cortisol concentration.

In summary, after for control for postnatal variables, either maternal interactive sensitivity, dyadic adjustment or postnatal levels of prenatal variables (e.g., maternal anxiety), the association between prenatal, programming variables that are observed in bivariate correlations remain significant, suggesting the presence of prenatal programming as an important developmental process. Postnatal variables appear to add very little information to our understanding of developmental outcome at 3 months.

Discussion

The purpose of this study was to examine the relative contributions of prenatal and postnatal factors to infant cognitive and emotional development at 3 months of age. A number of reports have highlighted the potential for foetal programming based on studies of maternal stress, smoking and drug and alcohol use during pregnancy. In most cases, however, these reports did not appropriately account for important postnatal factors that also have been shown to be linked to development, notably the quality of maternal interactive behavior, as well as different dimensions of family functioning such as marital adjustment. Likewise, previous research on such postnatal factors rarely took into account the potential contributions of prenatal variables. The current study attempted to consider both classes of variables in predicting early infant developmental outcome.

A novel aspect of the current study was its attempt to integrate an experimental design, where prenatal factors were manipulated by way of prenatal intervention strategy. Such manipulation allows for causal inference in a way that is not possible in correlational designs, even when they are longitudinal.

Finally, within this context, one of the objectives of the study was to test the validity of a specific prenatal intervention strategy to help mothers who experience stress and who may have difficulty with smoking, alcohol or drug use.

There are four elements of the results that we wish to underline and discuss.

1. Foetal programming.

The present results show some evidence for foetal programming. Several aspects of maternal prenatal stress/anxiety, smoking and alcohol use were significantly or marginally linked to infant cognitive or emotional development, as indexed by Bayley assessments and salivary cortisol concentrations. In this perspective, the current results are coherent with findings in other reports (e.g., Keenan et al., 2007; O'Connor, 2003; Weinstock, 2008). Moreover, these relations remained after accounting for variance attributed to postnatal factors (maternal sensitivity and marital adjustment).

The most important relations were found between the frequency of alcohol consumption and salivary cortisol concentration levels and change in cortisol concentration, suggesting that alcohol consumption has a strong foetal programming potential, perhaps particularly on the HPA-axis. These results are fully coherent with research by Jacobsen and colleagues (1999), Ramsay et al. (1996) and others who have found that higher levels of salivary cortisol were linked with alcohol consumption during pregnancy.

Maternal anxiety, assessed via the Symptoms Checklist, also appeared to be meaningfully linked to infant cognitive development and attention, in a manner related to that observed by van den Bergh and her colleagues (Mennes et al., 2009; van den Bergh, 2005). Major life events were marginally linked to attention. Taken together, these results provide support for the notion that maternal experience during the pregnancy period may be involved in foetal programming. That the assessments of development took place a full 30 weeks after the measures of anxiety and life events were taken is noteworthy. Finally, a marginal, inverse association between smoking (yes/no) and change in cortisol concentration was also found.

Overall, the different associations between prenatal variables and infant outcome lend support to the basic hypothesis that different aspects of the intrauterine environment may act on the foetus in a way that may be difficult to modify in the postnatal environment. and argue strongly for effective prenatal intervention aimed at groups which are at high psychosocial risk. The critical aspect of these finding is that they remained even after controlling for post-natal levels of the same variables and two important aspects of the mother-infant dyad's immediate environment. Thus, evidence for programming remained after control for important postnatal factors. However, the results suggest that the specific mechanisms linking different aspects of development together and with prenatal events are not well known. It is unclear why, in the current study, maternal anxiety (and to a lesser degree, life events) was associated with Bayley assessments but not cortisol secretion. It is not clear why the frequency of alcohol use was only related to cortisol secretion, but not to other developmental outcome variables. Such findings indicate that "programming" processes may differ as a function of prenatal variables and post-natal developmental outcome. Stress variables, consumption variables and other factors not presently included in the present study (e.g., environmental toxic substances) may act on different developmental processes.

Evidence of prenatal programming was not pervasive, however. A number of expected links were not found, notably between the frequency of cigarette smoking, drug use and development as well as between measures of psychological stress and development. The absence of results raises some of this study's limitations, to be addressed below. As well, they underline the importance of tapping into programming constructs through multiple measures.

2. Intervention effectiveness

Much of the demonstration we hoped to make in this study depended on the effectiveness of the proposed intervention strategy to change levels of prenatal factors related to stress or consumption. Our intervention strategy proved ineffective in this regard. Three factors may be important to consider. First, the intervention strategy was partly geared to addressing issues of consumption. Even though participating mothers used drugs, alcohol and smoked at expected levels, we were surprised that very few of them believed that this type of consumption may create difficulties for the foetus. In this context, it is possible that our intervention visits were too interspersed to be truly effective on this level. More frequent visits and contact with mothers may help make mothers more aware of the potential for harmful consumption on their part. Thus, it is possible that we did not have the intensity of intervention that is required with the kind of moderately high risk families involved in this study.

Second, it is possible that by addressing both stress and consumption, it was difficult to remain highly focused during the intervention process. Indeed, it is possible that by specifically addressing one topic or the other, effectiveness might have increased, as has been suggested in other intervention studies that have addressed specific issues of parenthood (Bakermans-Kranenburg et al., 2003). Attempting to be too exhaustive, in a limited number of visits, may not be an effective approach in the context of moderately high-risk parents. Both these issues, intervention frequency and focus, will need to be meaningfully addressed in future analysis of this data and other research work.

Third, the study reveals some of the limitations of the manner in which the randomization procedure was carried out. Randomization should have provided two groups that did not differ with respect to the factors that were the target of the intervention. However, some of the consumption variables were different between the two groups, with the intervention group being somewhat favoured. It is possible that the intervention was ineffective specifically because mothers in this group reported lower levels of smoking and drinking and that at such low levels, intervention effects are difficult to document. Thus, there appeared to be systematic differences between the intervention and control groups in spite of randomization, and these differences may have hindered our ability to show meaningful effects with the intervention strategy that was used.

Such differences are difficult to predict and they constitute an important limitation to the current findings. Future work of this kind may match groups on the basis of the consumption characteristics of mothers, prior to the beginning of the intervention.

Since the intervention did not prove to be effective, it was not possible to examine potential, methodological causal links between prenatal variables and infant outcome and, in this regard, we reverted to the usual regression strategies with correlational results to question the data as to the relative contributions of pre and postnatal factors.

That the intervention proved helpful with regard to infant attention suggests that there may be aspects that were effective, that mediated change on a level not currently investigated and that require identification. It will be important to continue to question the data in this regard to determine if there was a prenatal variable that did change in relation to the development of infant attention.

3. Postnatal variables

Perhaps the most intriguing finding in the current study is the absence of an association between all post-natal variables, maternal interactive sensitivity, marital adjustment and infant developmental variables. In effect, the correlations between most prenatal and post-natal variables were non-significant, which was very surprising. In previous work, we have documented that maternal sensitivity significantly predicted indices of socio-emotional and cognitive development at 6, 10 and 36 months in high risk groups (Lemelin et al., 2006; Tarabulsy et al., 2003; 2008; 2009) and previous research by other authors has shown the importance of marital relationships in predicting different indices of development (Amato & Keith, 2001). Several authors have also shown how caregiving can be linked to different aspects of emotional regulation, including HPA-axis functioning (Gunnar & Fisher, 2006). In effect, the absence of results in this area serves to emphasize prenatal variables over the potential contributions of post-natal variables. While there can be no doubt that prenatal variables contribute to later development (Weinstock, 2008), the present results should be interpreted in light of general results in the field, and not taken to indicate that post-natal factors have little consequence for early development.

4. Limits and sources of error

Small sample size.

The novel aspect of this study was the inclusion of an experimental group to target specific causal hypotheses. In the work we have conducted with different randomized control designs, we have learned that intervention work takes much of the financial resources dedicated to a study and almost always reduces the number of participants that can be recruited. The present study was no different. On several occasions, we would have hope to have more statistical power to more finely test the effectiveness of the program or potential moderating variables. A larger number of participants at the outset would also have proved helpful given the somewhat larger than expected attrition rate we experienced

Time of developmental assessment.

Developmental research has repeatedly shown that earlier assessments may well be the least reliable. It is possible that some of the difficulty we have had in establishing relationships between different variables and developmental outcome has to do with the reliability of developmental assessment conducted when infants are 3-months-old. It is also conceivable that effects on infant development may take more time to manifest themselves. It will be critical to follow-up the samples to determine if other assessments conducted a few months later show any signs of intervention effectiveness.

Focus of developmental assessment.

In the current study, developmental outcome was measured by one general assessment (Bayley Scales) and a more specific assessment of HPA-axis functioning. Other aspects of development might have been targeted. From a cognitive perspective, it might have been helpful to address different aspects of information processing (habituation, visual expectancy, contingency detection, etc.) or finer grained measures of infant attention. Likewise, other, more behavioural aspects of emotional development might have been examined. Arm-restraint tasks (i.e., frustration), or reactions to novelty are some of the tasks that address some of these issues.

High-risk vs. moderate risk participants.

Some decisions were made to ensure that the current project could be completed within the given time-line provided by the funding organisation. One of the aspects of this study most influenced by time considerations was the recruitment of participants. While the sample could be considered at moderate risk and included some high-risk mothers, it is possible that the number of high-risk mothers was not as well distributed in both groups as we might have hoped. Further, it is possible that intervention effects are perhaps more easily shown with groups that are at somewhat higher. Olds (Olds et al., 2007) has shown that in some cases, prevention efforts may have a more meaningful impact on higher risk families who perceive that they have more to gain from prevention than moderate risk mothers who do not perceive potential problems. In line with this suggestion is the repeated observation with current participants that substance use or stress were not really issues that needed specific attention had relatively little variance (in the case of substance use) and thus, little potential to show relations with other study variables. Again, further analyses, continued work with this type of group, increased sample sizes and longitudinally follow-up may help shed some light on this issue.

Conclusion

The present study underlines the importance of foetal programming as a developmental process that requires the attention of both scientists and practitioners. Moreover, there is the suggestion that there may be different kinds of foetal programming, some that are more closely related to stress, others that involve substance use. However, the present study also underlines the difficulty of changing maternal behavior during the prenatal period, above the change that almost all mothers readily engage in once they know they are pregnant. The ineffectiveness of the intervention strategy was a disappointment to all who were involved in the current study.

Further analyses of the data base and continued follow-up will be necessary to help elucidate some of the questions that emanate from this work, regarding the reasons for the ineffectiveness of the intervention and the relations (and absence of relations) that were found. It is hoped that this work will help establish a more effective intervention strategy for this critical period of human development.

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Table 2.
Socioeconomic and demographic information for mothers in intervention and control groups prior to intervention (n=38 per group).

Variable	Intervention group	Control group
Maternal age	21,78 (sd=2,11)	21,94 (sd=2,01)
% finished high school	52,63%	63,16%
Paternal age	25,92 (sd=3,88)	24,87 (sd=2,60)
% separated-divorced	5,27%	0,00%
Annual family income	Between 40 000$ and 50 000$	Between 40 000$ and 50 000$
Infant sex	19 boys/19 girls	18 boys/20 girls

No significant differences between groups on any variable.

Table 3.
Pre and post-intervention and postnatal variable means for intervention (n=36) and control (n=31) groups.

Variable	Intervention group	Control group
Maternal stress – pre-intervention	31.31 (sd=11.38)	31.03 (sd=9.51)
post-natal	29.36 (sd=8.19)	30.65 (sd=7.79)
Maternal anxiety – pre-intervention	.61 (sd=.64)	.68 (sd=.65)
post-natal[a]	.36 (sd=.62)	.65 (sd=.72)
Life events – pre-intervention	3.39 (sd=2.22)	2.77 (sd=2.38)
post-natal	3.22 (sd=1.69)	3.87 (2.14)
Smoking (%yes) – pre-intervention[a]	13.89	32.25
post-intervention	25.00	25.81
post-natal	35.48	34.49
Smoking (cigarettes/day) – pre-intervention	.72 (sd=2.54)	1.81 (sd=3.14)
post-intervention	.92 (sd=2.76)	1.65 (sd=3.37)
post-natal	1.97 (sd=4.08)	1.77 (sd=3.77)
% Alcohol use (%yes) – pre-intervention	66.67	70.97
post-intervention	91.66	90.32
post-natal	77.78	80.65
Alcohol use (frequency) – pre-intervention*	1.28 (sd=.74)	1.94 (sd=1.61)
post-intervention[a]	1.41 (sd=1.23)	2.03 (sd=1.49)
post-natal	2.44 (sd=1.71)	2.81 (sd=1.66)
Drug use (%yes) – pre-intervention	8.33	16.12
post-intervention	8.33	12.90
post-natal**	9.68	40.00
Drug use (frequency) – pre-intervention	.61 (sd=3.03)	1.90 (sd=8.97)
post-intervention	.81 (sd=3.55)	.35 (sd=1.05)
post-natal[a]	.25 (sd=0.94)	1.29 (sd=3.05)
Maternal Sensitivity	.62 (sd=.20)	.53 (sd=.26)
Marital Adjustment	123.83 (sd=10.10)	127.27 (sd=8.95)

a: $p<.10$
* $p<.05$
** $p<.01$

Table 4.
Bivariate correlations between pre-intervention and developmental outcome variables.

Prenatal Variable	Infant cognitive development	Infant attention	Mean salivary cortisol concentration[a]	Change in cortisol concentration[b]
Maternal stress	-.11	-.10	-.00	-.05
Maternal anxiety	-.26*	-.27*	.17	.02
Major life events	-.12	-.22[c]	-.20	-.05
Smoking (yes/no)	-.04	-.06	-.23	-.31[c]
Smoking (cigarettes/day)	.02	-.10	-.10	-.05
Alcohol use (yes/no)	-.01	-.10	.28	.28
Alcohol use (frequency)	-.08	-.01	.44**	.50**
Drug use (yes/no)	.10	.05	-.14	-.10
Drug use (frequency)	-.12	-.11	-.14	-.10

a. n=31; correlations covary for time of assessment
b. Concentrations in first assessment minus concentrations in second assessment.
c. $p<.10$
* $p<.05$
** $p<.01$

Table 5
Summary of hierarchical multiple regression testing for prediction of infant cognitive development by maternal prenatal anxiety after controlling for postnatal maternal anxiety, maternal interactive sensitivity and marital adjustment.

Variable	B	Standard error	Beta	t	p
Block 1					
Intercept	108.72	16.04	0.00	6.78	.0001
Post-natal Maternal Anxiety	1.59	1.76	0.11	0.90	ns
Maternal Sensitivity	6.00	5.00	0.15	1.20	ns
Marital Adjustment	-0.15	0.12	-0.15	-1.23	ns
Block 2					
Maternal prenatal anxiety	-3.64	1.79	-.24	-2.04	.05

($F(4,66)=2.15$, $p<.10$) model $R^2=12.20\%$

Table 6
Summary of hierarchical multiple regression testing for prediction of infant attention by maternal prenatal anxiety after controlling for postnatal maternal anxiety, maternal interactive sensitivity and marital adjustment.

Variable	B	Standard error	Beta	t	p
Block 1					
Intercept	40.93	6.60	0.00	6.20	.0001
Post-natal maternal anxiety	0.20	0.72	.04	0.28	ns
Maternal Sensitivity	0.25	2.06	0.04	0.12	ns
Marital Adjustment	-0.04	0.05	-0.09	-0.72	ns
Block 2					
Prenatal maternal anxiety	-1.58	0.73	-.27	-2.16	.05

($F(4,65)=1.36$, ns) model $R^2=8.20\%$

Table 7
Summary of hierarchical multiple regression testing for prediction of infant attention by maternal prenatal life events after controlling for postnatal life events, maternal interactive sensitivity and marital adjustment.

Variable	B	Standard error	Beta	t	p
Block 1					
Intercept	40.69	6.36	0.00	6.39	.0001
Major Life Events Post-natal	0.19	0.25	0.10	0.77	ns
Maternal Sensitivity	0.09	2.05	0.01	0.04	ns
Marital Adjustment	-0.04	0.05	-0.10	-0.78	ns
Block 2					
Major Life Events Prenatal	-0.40	0.21	-.24	-1.92	.06

(F(4,65)=1.25, ns) model R^2=7.57%

Table 8
Summary of hierarchical multiple regression testing for prediction of change in infant salivary cortisol concentration by prenatal smoking, after controlling for postnatal smoking, maternal interactive sensitivity, marital adjustment and time of saliva sampling.

Variable	B	Standard error	Beta	t	p
Block 1					
Intercept	1.30	2.78	0.00	0.47	ns
Time	0.14	0.61	0.04	0.23	ns
Block 2					
Post-natal smoking	3.72	3.58	0.22	1.04	ns
Maternal Sensitivity	1.80	7.56	0.05	0.24	ns
Marital Adjustment	0.11	0.19	0.12	0.58	ns
Block 3					
Prenatal smoking	-9.51	5.08	-.40	-1.87	.10

(F(5,30)=0.99, ns) model R^2=18.41%

Table 9
Summary of hierarchical multiple regression testing for prediction of change in infant salivary cortisol concentration by frequency of prenatal alcohol use, after controlling for postnatal frequency of alcohol use, maternal interactive sensitivity, marital adjustment and time of saliva sampling.

Variable	B	Standard error	Beta	t	p
Block 1					
Intercept	-24.92	23.75	0.00	-1.05	ns
Time	0.07	0.57	0.02	0.12	ns
Block 2					
Alcohol use Post-natal	-0.20	0.87	-.05	-0.24	ns
Maternal Sensitivity	-1.18	6.13	0.03	-0.19	ns
Marital Adjustment	0.16	0.17	0.18	0.94	ns
Block 3					
Alcohol use Prenatal	5.06	1.62	0.55	3.13	.01

($F(4,30)=2.06$, ns) model $R^2=29.13\%$

Table 10
Summary of hierarchical multiple regression testing for prediction of mean infant salivary cortisol concentration by prenatal alcohol use, after controlling for postnatal frequency of alcohol use, maternal interactive sensitivity, marital adjustment and time of saliva sampling.

Variable	B	Standard error	Beta	t	p
Block 1					
Intercept	8.11	2.93	0.00	2.77	.01
Time	-0.16	0.64	-0.05	-0.26	ns
Block 2					
Alcohol use Post-natal	0.48	1.46	0.10	0.45	ns
Maternal Sensitivity	-0.59	7.32	0.02	-0.08	ns
Marital Adjustment	0.13	0.21	0.13	0.62	ns
Block 3					
Alcohol use	4.84	1.75	0.50	2.76	.01

($F(5,30)=1.65$, ns) model $R^2=24.79\%$