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Tutkimusaiheeni on äidin raskaudenaikaisen ja synnytyksen jälkeisen stressin yhteys lapsen infektioherkkyyteen. Tarkoituksena oli selvittää raskaudenaikaisen stressin yhteyttä lääkärikäyntien, imeväisen infektioiden ja antibioottihoitojen määrään. Lisäksi oletin, että raskaudenaikainen ja synnytyksen jälkeinen stressi lisäisi terveyspalveluiden käyttöä.

Tutkimusaineisto oli FinnBrain-syntymäkohortin pilottiaineisto. Tutkimushenkilöt rekrytoitiin neuvoloista ultraäänitutkimusten yhteydessä raskausviikoilla 18–20 ja tutkimusaineisto kerättiin kotiin lähetettävillä kyselykaavakkeilla raskausviikoilla 18–22, 32–34 sekä lapsen ollessa 3 kk:n ja 6 kk:n ikäinen. Selittävinä muuttujina käytettiin EPDS- (masennus), PSI- (vanhemmuuteen liittyvä stressi), STAI- (ahdistus) ja PRAQ- (raskauteen liittyvä ahdistus) kyselyä sekä infektioiden, antibioottihoitojen ja lääkärissä käyntien määrää. Tutkittavat olivat 19–43-vuotiaita (keskimäärin 29,9), ja lisäksi heidän koulutustasonsa, tupakointi ja synnyttäneisyys otettiin huomioon sekoittavina tekijöinä.

Tutkimuksessani ei löytynyt yhteyttä äidin raskaudenaikaisen stressin ja alle kolmen kuukauden ikäisten imeväisten infektioiden määrän välillä. Sen sijaan kävi ilmi, että äidit, jotka kokivat tavallista enemmän vanhemmuuteen liittyvää stressiä, veivät lastaan useammin lääkäriin. Lapsilla ei kuitenkaan ollut enemmän infektioita tai antibioottikuureja verrattuna niiden lasten äiteihin, jotka olivat vähemmän stressaantuneita. Lisäksi äidit, joiden vauvat sairastivat tavallista enemmän infektioita, kokivat saavansa vähemmän sosiaalista tukea. Valituilla sekoittavilla tekijöillä ei ollut yhteyttä selittäviin muuttujiin.

Tutkimusaineisto oli pieni ja hypoteeseja tulisi testata suuremmassa aineistossa tuloksen varmistamiseksi. Tutkittavat, jotka jäivät pois tutkimuksen edetessä, olivat alemmasta sosioekonomisesta ryhmästä ja heillä oli korkeammat masennuspisteet, joten on mahdollista, että aineisto oli tässä suhteessa vinoutunut. Tämä saattoi osaltaan vaikuttaa tuloksiin. Äidit, jotka ovat stressaantuneita, saattavat hakea sosiaalista tukea terveydenhuollosta ja intervention olisi mahdollista auttaa heitä ja vähentää terveydenhuollon kustannuksia.

Asiasanat: raskaudenaikainen stressi, vanhemmuuden stressi, imeväisen infektiot

Does Stress Predict Infant Infections and the Use of Health Services in Families with 6-Month-Old Infants - the FinnBrain Pilot Study

Stress is a major environmental factor that affects the well-being of children and parents (Manning et al, 1996, Pechtel et al, 2011). The concept of stress is heterogeneous and implies alterations in homeostasis due to a variety of stimuli or exposures. When a person's emotional or physical capacity to cope is exceeded, they experience stress, which if prolonged can lead to a large variety health problems. (Gunnar & Quevado, 2007.) Early life stress is understood as child's exposure to stressors in early childhood that leads to prolonged stress (Brown et al, 2009). While early life stress has been shown to increase the risk of psychiatric disorders (Green et al, 2010), it has also been associated with increased risk of physical illnesses later in life (McFarlane, 2010). In adults work stress is related to increased risk for respiratory infections (Runeson-Broberg et al, 2014). Increased vulnerability for infections has also been suggested as a result of early life stress exposure (Belliger et al, 2008). Stress during pregnancy can be considered as a form of early life stress exposure and it may have programming effects with long-lasting health effects across the life span (Lupien et al, 2009; Merlot et al, 2008). For example untreated maternal mood symptoms during pregnancy associate with short- and long-term emotional and physical problems in the foetus, but also later in the newborn, child and adolescent (Gentile 2015).

It has been shown in both animal and human studies that pre- and postnatal psychosocial stress has an unfavourable effect on the offspring (Avitsur et al, 2015). In animals, prenatal stress lowers the levels of protective microflora in infants and may increase the risk for postpartum infections in monkeys (Bailey et al 2004). Prenatal stress can be experienced in association with for example maternal anxiety and depression symptoms, pregnancy-specific anxiety or psychosocial stressors (e.g. bad relationship with partner) all of which have been shown to predict negative infant outcomes (O'Connor et al, 2003; Huizink et al, 2002; Bergman et al, 2007). Not many studies have been made on the subject of stress and infections, but human studies are accumulating and suggest that life and emotional stress during pregnancy are associated with an increased risk of infection and other paediatric diseases (Tegethoff et al, 2011). In a study by Phelan et al (2015) high prenatal stress predicted maternal reporting of infant illness in the first year of life. Another research shows that unsatisfactory prenatal marital quality and stressful life events both had a significant association with the number and variety of parent-reported infections in infants during their first year (Henriksen et al, 2015). It is clear that larger maternal stress factors, such as serious life events during the prenatal period, may have an impact in child development, but it seems that also exposure to seemingly milder and often chronic stressors seem to have an effect on infant neurodevelopment and health (Eunjeong et al, 2015; Gentile 2015). It has been thought that epigenetic mechanisms are at least partly the mediators of the effects of prenatal stress on foetuses and that the main regulator of stress response, the hypothalamic-pituitary-adrenal (HPA) axis is one of

the main targets of this programming. A meta-analysis by Palma-Gudiel et al (2015) shows that there is an association with DNA methylation of the glucocorticoid receptor gene and prenatal stress.

An excellent proxy for health problems is the use of healthcare resources. Serious life stressors in adult life reportedly associate with the frequency of doctoral visits and overnight hospitalization (Gawronski et al 2014). National population-based study in Denmark showed increased utilisation of primary healthcare in persons exposed to severe stress in prenatal life (Nielsen et al, 2012). Psychosocial problems have an association with frequent health care use in adolescents and adults (Kekkonen et al 2015; Joukamaa et al, 1996). An earlier Finnish study showed that family factors may be associated with frequent medical consultations and recurrent antibiotic treatment of infants (Louhi-Pirkanniemi et al, 2004). Prenatal psychosocial stress has been shown to increase use of health care (Phelan et al 2015). Their study showed that maternal prenatal stress caused mothers to take their children to urgent and emergency care units, but high prenatal stress did not predict hospitalization. This suggests that maternal stress correlates with maternal health behaviour rather than the medical emergency of the child. Parenting stress might be linked to the use of health care services. In an older study (Abidin, 1983) there was no significant difference between parents' level of stress, measured by the Parenting stress index (PSI), and paediatric medical utilization for the first 18 months postnatal. Later in the US (Raphael et al, 2010) a connection was found between high parenting stress and tendency to seek emergency care for their children when compared to families with low parenting stress.

The objective of our study was to determine if maternal prenatal stress predicts the number of infections in their infant children. Further, we aimed to analyse whether there is an association between postnatal stress and the number of infant infections, antibiotic prescriptions and the frequency of doctoral visits. We expected that higher maternal prenatal stress would have an increasing effect on the number of infections in the offspring. We also hypothesised that parenting stress would increase the frequency the infants were taken to the doctor.

METHOD

Study population

The study population is the pilot of the FinnBrain Birth Cohort Study (www.finnbrain.fi). They were personally recruited in ultrasonography appointments from municipal maternity clinics in Turku, Finland between May and December 2010. In the beginning 254 families were asked to participate, 203 agreed, but in the end a total of N=157 mothers participated in the study and N=102 of them continued for at least 6 months after giving birth and were included in our study In all, N=55 were excluded for discontinuing the study before the 6 -month assessment. Those who discontinued were less educated (highly educated: 16.7 % vs. 40.2 %, p=0.000) and smoked more frequently during pregnancy (24.1 % vs. 8.8 %, p=0.014) than those retaining to the study. There was also higher frequency of elevated depression scores

in the group that discontinued (EPDS > 13 points: 9.1 % v 4.9 %, p=0.036). There was no age difference between the groups (p=0.147).
Background factors in our study population were assessed by using questionnaires. The demographic characteristics are presented in table 1. The age distribution of the participants varied from 19 to 43 years (mean 29.9 years, SD 4.87, SE 0.49) Education was classified as low (no academic degree), middle (up to lower academic degree) and high (master or doctor level) educational level. All of the participants gave their written informed consent. The Joint Ethics Committee of the University of Turku and Hospital District of Southwest Finland has approved the study protocol.

Measures

Self-report questionnaires were used assessing participants at gestational weeks 18-22 and 32-34 and after delivery at three months and six months.

We evaluated the mother´s depressive symptoms with the EPDS (Edinburgh Postnatal Depression Scale) questionnaire twice during pregnancy (week 18-22 and 32-34) and 3 months after delivery. It is a reliable (Cronbach´s alpha = 0,87) screening tool for assessing perinatal depression. Prenatal EPDSs were summed to a single variable using the average values of the two time points. EPDS has 10 questions each ranging from 0-3 points (Cox et al, 1987). EPDS score over 13 was used as a cut point for identifying risk for major depression, as it has been shown in earlier studies that 86 % of women who scored 13 or more points are diagnosed with minor or major depression (O'Hara et al 1996).

PRAQ-R (Pregnancy-Related Anxiety Questionnaire, Revised) was used to measure maternal anxiety related to pregnancy. It was assessed during pregnancy at 32-34 weeks. It has 10 questions ranging from 1 (definitely not true) to 5 (definitely true). The questionnaire measures three factors: Fear of giving birth (F1), Fear of bearing a handicapped child (F2) and Concern about one´s own appearance (F3) and a total score (Huizink et al, 2004).

PSI/SF + SPSQ (Parenting stress index-short form + Swedish Parenthood Stress Questionnaire) was used to measure parenting stress. PSI/SF is derived from the original PSI that has 101 questions. PSI/SF has 36 questions scores ranging from 1 (strongly agree) to 5 (strongly disagree) points. It is found to be reliable in assessing maternal stress (Cronbach's alpha 0,91 for the total score and 0,80-0,87 for the subscales). Like the original questionnaire it is divided into subscales: a Parent Domain that assesses the parent's distress in his or her role, and two Child Domains. One Child Domain assesses the child's behaviour and the other the parent's expectations of the infant. In this study we used the Parent Domain, which can be used to measure specific types of stress: impaired sense of parenting Competence, lack of Social Support, conflict in life Roles or with Spouse (Abidin, 1995). The SPSQ was developed from the Parenting Stress Index parent domain (Österberg et al, 1997). The questionnaire is a reliable (Cronbach´s alpha: 0,90 for total scale and 0,64-0,84 for the subscales) (Lagerberg et al, 2013) measures the experienced stress level of the parent as well as their perceived stress coping resources. The original questionnaire has 34 items that are scored from 1 (strongly disagree) to 5 (strongly agree). The higher the score the

higher is the experienced stress level. In this study a shorter version of the SPSQ was used containing 15 items. Subscales were spouse relationship problems, incompetence regarding parenthood and role restrictions. These questionnaires were combined as a single form. Data for PSI/SF and SPQS were collected 3 and 6 months after delivery. The subscales and the mean values were used in our study.

STAI (State Trait Anxiety Inventory) is a reliable (Cronbach's alpha 0,91) tool to measure general anxiety. It has 40 questions that measure momentary (state anxiety/20 items) and overall (trait anxiety/20 items) anxiety levels (Spielberg et al, 1983). The items are scored from 1 (not at all) to 4 (very much) In our study we used only the 20 state anxiety questions. It was assessed twice during pregnancy (18-20 weeks and 32-34 weeks) and 3 months after delivery. Prenatal STAI results were converted to a single sum variable using the average values of the two time points.

The parents reported visits to the doctor, infections and antibiotic treatments in health questionnaires. Visits to the doctor and antibiotics were asked at six months (Yes/No and How many in the past three months). The number of infections was asked at three months (Yes/No and How many in the past three months). The number of infant infections, prescription on antibiotics, and frequencies of doctoral visits are presented in Table 1. One quarter of the infants had had at least one infection by three months, while one third had visited a doctor. A smaller proportion (10.9%) had been prescribed antibiotics.

RESULTS

Data from the questionnaires EPDS, STAI, PRAQ and PSI is described in table 2.
In our study, maternal prenatal stress did not predict infant infections during the first three months (table 3). Neither anxiety nor depression symptom scores were related to infant health. However, we did observe that there is an association between parenting stress and the frequency of doctoral visits as well as the amount of infant infections. Mothers who felt more stressed ($p=0.044$) or insufficient as parents ($p=0.048$) at three months took their children to see the doctor more often during the time between four to six months after childbirth than mothers who had less stress. The mothers whose children had more infections at three months felt they lacked social support ($p=0.038$) at six months.
The number of treatments with antibiotics did not associate with the frequency the children were taken to see the doctor. Potential confounding variables; maternal or paternal age, education or smoking, did not associate with dependent variables.

Discussion

Contrary to our hypothesis, we did not find a connection between pre- or postnatal parental stress and increased infections in infants. However, we noted a connection between postnatal stress and increased frequency of doctoral visits, although the number of infections or antibiotic treatments were not related to prenatal or

parenting stress. Mothers who experienced more stress and felt less competent as parents in the first three months after delivery were more prone to take their child to the doctor. Also the mothers whose child had infections in early life felt stressed by the lack of social support. Our results are supported by the recent larger study by Phelan et al (2015) that showed psychosocial stress during first pregnancy predicts maternal reporting of infant infectious disease and urgent care and emergency department visits but did not predict hospitalization, suggesting that maternal stress increases the visits to health care providers but does not increase infections that require hospital treatment. Health care usage by families with young children and its association with stress has not been adequately researched and more studies are required to confirm these findings.

While our main hypothesis was not supported by our results, other larger studies have had opposite outcomes. The national cohort study by Tegethoff et al (2011) clearly shows a statistical association between prenatal stress and childhood paediatric disease, though the associations were of low to moderate strength. The large Norwegian cohort by Henriksen and Tuhen (2015) also shows an association between infant infectious disease and stressful life events as well as relationship dissatisfaction in pregnancy. The results were stronger between infections and relationship problems (OR 1.03-1.35) than between infections and stress (OR 0.99-1.17). Overall, not many studies have been made of this subject and the majority of them are of a large study population. The effect of prenatal stress on the risk for infections is more likely to be of a weak to moderate level, which may explain why we did not reach the same conclusions in our smaller study population.

Mothers who experience more stress might seek support from visits to the doctor as they may feel they are not getting adequate support otherwise. There was no association between stress and number of antibiotic prescriptions, possibly indicating that the children were not given unnecessary treatment. This is important as it has been shown that antibiotics also have negative effects on children's health (Bailey et al, 2014; Metsälä et al, 2015) and should not be used excessively. Comparing these findings to an earlier study, a positive change in practices is suggested in terms of treating infections in young children (Louhi-Pirkanniemi et al, 2004).

This cohort was recruited from maternity clinics that are used by essentially all mothers in Finland. The data is limited due to small study group and the results should be further tested with a larger sample size. The small sample size further precluded more sophisticated multivariable modelling but the most important cofounders were not observed to associate with the major variables in this population. Also in our study a high number of mothers discontinued and among them were mothers of lower socio-economic status and higher depression scores. This might have diluted our results as people with lower socio-economic status have more health problems (Kastorini et al, 2015). The number of infections was acquired with questionnaires filled by mothers and were not confirmed by doctors. This may cause the diagnosis to be less reliable than if the data was gathered from clinics or registers.

There is only a handful of studies about prenatal stress and infections in offspring. This could be partly due to publication bias. Nevertheless there are large, reliable studies that have shown this association and the topic should be further researched to

strengthen the hypothesis. Since it has been shown that maternal depression and anxiety can be a target for a successful intervention, it is possible to lower the costs of primary health-care by giving support to these women who feel more stressed and lack social support (de Camps Meschino et al, 2015).

Tables

Table 1: Charasteristics of the Study Subjects (n=102)		n/%
Education		
	Low	23/22.5
	Middle	33/32.4
	High	41/40.2
	unanswered	5/4.9
Smoking		
	pregnant	9/8.8
	postnatal	7/6.9
Primiparous		
	yes	63/61.8
	no	33/32.3
	unanswered	6/5.9
Infections		
	no	47/46.1
	1 or more	27/26.5
	unanswered	28/27.5
Antibiotics		
	yes	11/10.9
	no	91/89.2
Visits to a doctor		
	no	69/67.6
	1	21/20.6
	2 or 3	12/11.8

Table 2: Descriptions of maternal prenatal stress and parenting stress measures (n=102)

	N	Mean	Median	SE	SD	Range
PRAQ (Mean)	92	24.1	23.5	0.82	7.87	(10.0-50.0)
PSI (Mean) 3 Mo	95	2.47	2.40	0.05	0.46	(1.53-3.80)
PSI (Competence) 3 Mo	95	2.19	2.17	0.06	0.58	(1.00-3.50)
PSI (Role) 3 Mo	95	3.34	3.25	0.07	0.72	(1.50-5.00)
PSI (Spouse) 3 Mo	95	2.09	2.00	0.07	0.65	(1.00-3.80)
PSI (Support) 3 Mo	95	3.28	3.20	0.06	0.54	(1.40-4.50)
PSI (Mean) 6 Mo	101	2.48	2.47	0.04	0.45	(1.60-3.47)
PSI (Competence) 6 Mo	101	2.18	2.17	0.06	0.60	(1.00-4.00)
PSI (Role) 6 Mo	101	3.37	3.25	0.06	0.61	(2.25-5.00)
PSI (Spouse) 6 Mo	101	2.14	2.00	0.07	0.71	(1.00-4.60)
PSI (Support) 6 Mo	101	3.17	3.20	0.05	0.55	(1.70-4.40)
EPDS (Mean total score across pregnancy)	102	4.74	4.00	0.33	3.30	(0.00-15.0)
EPDS (Mean) 3 Mo	102	4.57	4.00	0.37	3.73	(0.00-17.0)
STAI (Mean total score across pregnancy)	101	30.9	29.0	0.66	6.60	(21.0-56.5)
STAI 3 Mo	97	31.5	30.0	0.77	7.61	(20.0-55.0)

PRAQ= Pregnancy-Related Anxiety Questionnaire, PSI=Parenting Stress Index, PSI Subscales: Competence=Impaired Sense of Parenting Competence, Role=Conflict in Life Role, Spouse=Conflict With Spouse, Support= Lack of Social Support, EPDS=Edinburgh Postnatal Depression Scale, STAI=State Trait Anxiety Scale, Mean total score across pregnancy =Gestational Week 18-22 and 32-34 Sum Variable, Mean=Mean Score of All Questions, 3 Mo=Three Month Questionnaire, 6 Mo=Six Month Questionnaire

Table 3:
The associations (Mann-Whitney U Test) between maternal prenatal stress and parenting stress and the frequency of infections, antibiotics treatment, and doctoral visits (n=102), P-values

	Visits to the Doctor 4-6 months old, frequency	Infections first 3 months of life, frequency	Antibiotics 4-6 months old, frequency
PSI (Mean) 3 Mo	0.044	0.74	0.06
PSI (Competence) 3 Mo	0.048	0.87	0.06
PSI (Role) 3 Mo	0.19	0.62	0.89
PSI (Spouse) 3 Mo	0.72	0.99	0.24
PSI (Support) 3 Mo	0.66	0.14	0.50
PSI (Mean) 6 Mo	0.52	0.08	0.41
PSI (Competence) 6 Mo	0.57	0.40	0.52
PSI (Role) 6 Mo	0.70	0.26	0.87
PSI (Spouse) 6 Mo	0.86	0.30	0.48
PSI (Support) 6 Mo	0.95	0.038	0.85
PRAQ	0.92	0.49	0.58
EPDS (Mean total score across pregnancy)	0.27	0.91	0.75
EPDS 3 Mo	0.18	0.17	0.24
STAI (Mean total score across pregnancy)	0.61	0.74	0.46
STAI 3 Mo	0.42	0.87	0.16

PRAQ= Pregnancy-Related Anxiety Questionnaire, PSI=Parenting Stress Index, PSI Subscales: Competence=Impaired Sense of Parenting Competence, Role=Conflict in Life Role, Spouse=Conflict With Spouse, Support= Lack of Social Support, EPDS=Edinburgh Postnatal Depression Scale, STAI=State Trait Anxiety Scale, Mean total score across pregnancy sum=Gestational Week 18-22 and 32-34 Sum Variable, Mean=Mean Score of All Questions, 3 Mo=Three Month Questionnaire, 6 Mo=Six Month Questionnaire

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