Perinatal health epidemiology in multi-ethnic Amsterdam: psychobiological processes

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Summary

One of the main aims of this thesis was to explore perinatal health epidemiology in the multi-ethnic city of Amsterdam, the Netherlands. As described in Chapter 1, perinatal health epidemiology studies the health of mother and baby during pregnancy, birth and the early postpartum period. Important markers of an unhealthy intrauterine environment are perinatal mortality and morbidity; perinatal morbidity (e.g. preterm birth, low birthweight) could have important consequences for long-term health outcomes such as cardiovascular disease. Worldwide, perinatal mortality and morbidity rates differ between ethnic groups; this can, in theory, be explained by ethnic differences in a broad range of maternal risk factors during pregnancy. The first objectives of this thesis were to examine (a) the perinatal health outcomes among the main ethnic groups in Amsterdam, and (b) to what extent ethnic disparities in perinatal health outcomes could be explained by ethnic differences in maternal risk factors during pregnancy.

This thesis further focused on psychobiological processes involved in (ethnic disparities in) perinatal health outcomes. Maternal psychosocial problems during pregnancy may be an important risk factor for adverse perinatal health outcomes; a potential psychobiological pathway involves the hypothalamic-pituitary-adrenal (HPA) axis and the hormone cortisol. Evidence for the potentially adverse effects of maternal psychosocial problems is, however, inconsistent and research on the underlying psychoendocrinological pathway is scarce. Psychobiological processes involved in fetal and infant health outcomes also include fetal origins of infant psychosocial health. Excessive infant crying can be considered a reasonable indicator of infant psychosocial stress; fetal origins of excessive infant crying are largely unknown and more research is required. The third and fourth objectives of this thesis were to examine (c) the association between maternal psychosocial well-being during pregnancy (as indicated by self-report scales and the biomarker cortisol) and perinatal health outcomes, and (d) the association between maternal risk factors during pregnancy, in particular maternal nutritional status, and infant psychosocial well-being (as indicated by infant crying behavior).

To study the objectives of this thesis, data from the Amsterdam Born Children and their Development (ABCD) study were used. The ABCD study is a prospective cohort study that aims to explore the association between (ethnic differences in) maternal risk factors during pregnancy and (ethnic disparities in) perinatal and infant health outcomes. From January 2003 till March 2004, all pregnant women in Amsterdam (n = 12 373) were approached to enroll in the ABCD study at their first prenatal visit to an obstetric caregiver (± 12th pregnancy week). Women were asked to fill out a pregnancy-questionnaire covering sociodemographic information, lifestyle and (psychosocial) health (n = 8266; response rate 67%), and to donate a blood sample for the analysis of nutrients and hormones (n = 4389). Three months after delivery, women received a baby-questionnaire covering the (psychosocial) health of mother and baby (n = 5218). To enhance the inclusion of pregnant women from the main ethnic groups in Amsterdam, i.e. the Dutch, Surinamese, Antillean/Aruban, Turkish, Moroccan and Ghanaian group, questionnaires
were in Dutch, English, Turkish or Arabic and Turkish- or Arabic-speaking trained female interviewers were available for oral administration of the questionnaire. Perinatal health outcomes were available from the Amsterdam Youth Health Care Registration and the Dutch Perinatal Registration.

We started by studying perinatal health outcomes and potential risk factors among the main ethnic groups in Amsterdam. In Chapter 2, ethnic disparities in the birthweight distribution of term-born infants were explored and to what extent the disparities could be explained by ethnic differences in maternal risk factors during pregnancy. Because birthweight differences can be either constitutional (‘natural’ limited growth potential) or pathological (growth restricted), respectively the explanatory role of constitutional and environmental factors was examined. Ethnic groups were categorised into a Dutch group and first and second generation Surinamese, Antillean, Turkish, Moroccan, Ghanaian and other non-Dutch groups. Only singleton live births with ≥37.0 weeks gestation were included for analysis (n = 7118). Mean birthweight ranged from 3223 g (second generation Surinamese newborns) to 3548 g (Dutch newborns). Linear regression analysis showed that the ethnic minority groups had significantly lower mean birthweights compared to the Dutch group. Adjustment for constitutional factors (fetal gender, maternal age, parity, maternal height) substantially reduced the ethnic disparities in birthweight (corrected for gestational age), while adjustment for environmental factors (education, cohabitation status, maternal BMI, smoking, alcohol consumption, depressive symptoms, work stress) provided little additional explanation. The birthweight disparities between Dutch newborns and Turkish, Moroccan and other non-Dutch newborns could largely be explained by, in particular, the constitutional determinants, limiting the opportunities for prevention. On the contrary, birthweight disparities between the Dutch group and the first and second generation Surinamese and Ghanaian and first generation Antillean group could not be fully explained by the explored maternal risk factors; mean birthweights remained respectively 98, 159, 121 and 102 g lower. Future research should explore whether the unexplained birthweight disparities reflect pathological growth restriction or a constitutional limited growth potential, by searching for unexplored environmental factors, cumulative risk effects and genetic components, and by exploring weight-specific mortality and morbidity rates per ethnic group.

In Chapter 3, ethnic disparities in the prevalence of preterm birth (PTB) were explored and to what extent the disparities could be explained by ethnic differences in maternal risk factors during pregnancy. In addition, the effect of a cumulation of risk factors on ethnic disparities in PTB prevalence was explored. PTB (<37.0 weeks gestation) was divided into spontaneous preterm births (SPB) and iatrogenic (medically indicated) preterm births (IPB). Only singleton live births with ≥24.0 weeks gestation were included for analysis (n = 7604). Ethnicity was based on the country of birth of the pregnant woman’s mother: Dutch, Surinamese, Antillean, Turkish, Moroccan, Ghanaian, and other non-Dutch. In our sample, a mean PTB prevalence of 5.5% was observed, ranging from 4.1% (Moroccan group) to 11.0% (Ghanaian group); 68% was SPB, 20% IPB and 12% had an unknown subtype. Compared to the Dutch group, significant
ethnic disparities in PTB prevalence were not observed for the Turkish, Moroccan and other non-Dutch group; these groups even had a lower PTB risk. On the contrary, Surinamese, Ghanaian and Antillean women had a higher PTB risk, in particular for IPB with odds ratios of 2.1, 3.2 and 3.6 respectively after full adjustment [risk factors: maternal age, parity, maternal BMI, education, cohabitation status, maternal smoking, alcohol consumption, depressive symptoms, physical heavy work, previous obstetric complications (PTB, abortion, miscarriage/stillbirth), hypertensive disorder, and indicators of vaginal infectious disease]. Ethnic minority groups had a higher cumulation of risk factors (‘cumulative risk score’ ranging from 2.1 to 3.7) compared to the Dutch group (score of 1.8). Adjustment for the cumulative risk score considerably decreased the PTB risk among Surinamese, Ghanaian and Antillean women. The predictive accuracy of the cumulative risk score was, however, too low to be used for individual risk selection. In conclusion, the PTB risk of Dutch, Turkish, Moroccan and other non-Dutch women seemed favourable compared to the PTB risk of Surinamese, Antillean and Ghanaian women; this could potentially be explained by cumulative risk effects, unexplored risk factors, obstetric care practices or (epi)genetic influences.

Next, we studied the potentially negative effects of maternal psychosocial problems during pregnancy on perinatal health outcomes. In Chapter 4, we explored how maternal psychosocial problems relate to whether or not a woman continues to smoke during pregnancy. Only women who smoked before pregnancy were included in this study ($n = 1947$). Women were categorized as quitters (62%) or non-quitters (38%) based on their self-report of smoking behavior during early pregnancy. Non-quitters reported significantly higher levels of depressive symptoms, anxiety, pregnancy-related anxiety, job strain and physical/sexual violence, but not of parenting stress. After adjustment for maternal age, parity, ethnicity, education, cohabitation status, the amount of smoking before pregnancy, smokers in the environment and desirability of pregnancy, women with very low or high levels of pregnancy-related anxiety, exposure to physical/sexual violence or high job strain had a significantly higher risk for continued smoking during pregnancy. Although a causal relationship could not be verified because of the cross-sectional design of data collection, if confirmed, smoking cessation programs for pregnant women should include the management of psychosocial problems.

In Chapter 5, the association between maternal depressive symptoms during pregnancy and major perinatal health outcomes, i.e. preterm birth (PTB), small-for-gestational-age (SGA), Apgar score and child loss, was examined. In addition, it was examined whether the associations were mediated by maternal smoking during pregnancy and whether the associations differed between ethnic groups. Ethnic groups were categorized into a Dutch, Creole, Turkish and Moroccan group. Maternal depressive symptoms were measured by the validated Center for Epidemiologic Studies Depression scale (CES-D). Multiple births were excluded leaving a baseline sample of 8050 women for analysis. Thirty percent ($n = 2465$) of the women reported high levels of depressive symptoms. The prevalence of perinatal outcomes in our sample was: 5.4% (PTB), 12.3% (SGA), 1.5% (low Apgar score) and 1.4% (child loss), with a higher prevalence among women with high levels of depressive symptoms. After adjustment for maternal age, parity, ethnicity, education, pre-pregnancy BMI,
hypertension, alcohol and drug use and maternal smoking, high levels of maternal depressive symptoms were significantly associated with SGA and a low Apgar score, but not with PTB and child loss. The observed associations could possibly be explained by a psychoendocrinological pathway or through mediation by maternal risk behaviours such as smoking, poor nutrition, a lack of prenatal health care visits or the use of antidepressants. Interaction effects between maternal depressive symptoms and ethnic background on perinatal health outcomes were insignificant, however, stratified analysis by ethnic background suggested an excess risk for Creole women, possibly explained by higher vascular activity and reactivity to stress among blacks.

In Chapter 6, a potential psychobiological pathway into adverse perinatal health outcomes involving the hormone cortisol was explored. We examined the association of maternal cortisol concentration during pregnancy with maternal psychosocial problems and with fetal growth, as indicated by offspring birthweight and SGA risk. Total maternal cortisol concentration was determined in serum and standardized for time of day and gestational age at blood sampling. After excluding multiple births, preterm births, pre-gestational diabetes mellitus, steroid medication and gestational age at blood sampling >20.0 weeks, 2810 women were included in the analysis. We observed that a higher maternal cortisol concentration was associated with lower offspring birthweight and a higher SGA risk; the associations were, however, insignificant after adjustment for gestational age at birth, infant gender, ethnicity, maternal age, parity, maternal BMI and smoking. Stratified analysis for time of day at blood sampling suggested that the association was only present among cortisol concentrations in blood samples collected ≤09:00h (n = 94). Maternal cortisol concentration was unrelated to the level of maternal depressive symptoms, anxiety, pregnancy-related anxiety, parenting stress and job strain and exposure to physical/sexual violence. In conclusion, our data could not support the hypothesis that maternal psychosocial problems affect fetal growth through maternal cortisol levels. Our measurement of cortisol, however, left much to be desired. Future research should include multiple cortisol measurements at different time frames of the diurnal cortisol rhythm.

Lastly, we explored fetal origins of infant psychosocial well-being, as indicated by infant crying behavior. The origins of excessive infant crying are largely unknown; an early nutritional origin has not yet been explored. In Chapter 7, we examined the association of maternal vitamin B-12 and folate status during pregnancy with excessive infant crying. The amount of infant crying was reported by the mother a few months after birth and excessive infant crying was defined as crying ≥3 hours/day on average in the past week. Vitamin B-12 and folate concentrations were determined in serum and standardized for gestational age at blood sampling. Multiple births were excluded leaving 2921 (vitamin B-12) and 2622 (folate) women for analysis. In our sample, the prevalence of excessive infant crying was 3.4%. We observed a significant association between a low maternal vitamin B-12 concentration and excessive infant crying, also after adjustment for maternal age, parity, ethnicity, education, smoking and maternal psychological problems. Stratified analysis suggested a stronger association among women with high levels of depressive symptoms, anxiety and/or pregnancy-related anxiety during pregnancy. Maternal folate concentration was
not associated with excessive infant crying. We discussed two potential mechanisms through which vitamin B-12 may affect infant crying behavior: (1) vitamin B-12 and folate are involved in the methionine-homocysteine metabolism, which is essential in fetal neurodevelopment; (2) vitamin B-12 is involved in melatonin synthesis; excessive infant crying could be a symptom of an immature melatonin/sleep-wake rhythm; this could hypothetically be amplified by an immature cortisol rhythm caused by maternal psychological problems. In conclusion, this study provided first evidence for an early nutritional origin in excessive infant crying; further research is, however, necessary to support this preliminary evidence. If confirmed, prenatal checks of pregnant women should be extended with diagnosing and treating for vitamin B-12 deficiency.

In Chapter 8, we discussed the main findings presented in this thesis, methodological issues such as the operationalisation of ethnicity and maternal and infant psychosocial well-being, and implications for clinical practice such as the need for interventions covering psychosocial problems, multiple risk factors and cultural and language differences. Three main concluding points were made:

First, ethnic disparities in perinatal health outcomes were observed among the main ethnic groups in Amsterdam, i.e. the Dutch, Surinamese, Antillean, Ghanaian, Turkish and Moroccan group: mean offspring birthweight was lower among all ethnic minority groups compared to the Dutch group while the risk for PTB, a low Apgar score and child loss was only higher for the Surinamese, Antillean and Ghanaian group. Although the ethnic disparities could, to some extent, be explained by single conventional maternal risk factors during pregnancy, a cumulation effect of multiple risk factors – especially seen among the ethnic minority groups – seemed to provide a better explanation. It seems furthermore reasonable that (epi)genetic influences are involved as offspring from mainly African descent had unexplainable lower birthweights and a higher PTB risk. To reduce ethnic disparities in perinatal health outcomes, comprehensive antenatal health promotion programs should be developed and implemented that cover not only important proximal risk behaviors like smoking, poor nutrition and work stress, but also distal factors like lack of social support or financial problems. As long as there is no convergence in risk behaviors and their determinants between ethnic minority groups and the native Dutch group, we recommend the implementation of antenatal programs that account for cultural-specific beliefs and norms.

Second, one of the important risk factors for adverse perinatal health outcomes appeared to be maternal psychosocial stress. The prevalence of perinatal mortality and morbidity was higher among women who reported high levels of depressive symptoms during pregnancy, though only the prevalence of SGA and a low Apgar score appeared to be statistically significantly higher when adjusting for relevant covariates. The relationship between maternal psychosocial stress during pregnancy and offspring outcome could at first be ascribed to a small mediation effect of maternal smoking behavior. Alternatively, elevated levels of the stress hormone cortisol potentially influence fetal development, however, only limited evidence for this psychobiological pathway could be provided because of methodological difficulties related to the measurement of cortisol. While ethnic minority groups in our sample had a high prevalence of both psychosocial problems
and adverse perinatal health outcomes, differences in psychosocial well-being did not seem to be responsible for ethnic disparities in perinatal health outcomes. We hypothesized that pregnant women from African descent might be more susceptible for detrimental effects of psychosocial stress on offspring outcomes through ‘allostatic load’ and/or higher vascular (re)activity. As psychosocial stress is becoming a huge public health problem, obstetric caregivers should be aware of the potentially negative effects on fetal health. We recommend to screen pregnant women for psychosocial stress as part of routine antenatal care or preferably, as part of preconceptional care, provided that efficacious treatment programs are available.

Third, psychosocial stress in infancy as expressed by excessive crying behavior may have its origin during fetal development. Maternal nutritional status during pregnancy appeared to be of importance as an association was observed between a low vs. high maternal vitamin B-12 status during pregnancy and excessive crying behavior of the infant in the first months of life; this might, in theory, be ascribed to fetal (dys)maturation of the sleep-wake / melatonin rhythm. Although these observations offer opportunities for prevention and treatment of excessively crying infants, the preliminary results first need to be replicated, preferably with prospective measurements of infant crying behavior through diaries or audiotape recordings.