Perinatal health epidemiology in multi-ethnic Amsterdam: psychobiological processes

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Chapter 8

General discussion
Discussion of main findings

Main aims of this thesis were (I) to explore and explain disparities in perinatal health outcomes among ethnic groups in Amsterdam, the Netherlands, and (II) to elucidate psychobiological pathways into (ethnicity-related) perinatal and infant health outcomes. In this chapter, we will reflect on our main results and discuss them in the light of methodological issues and implications for clinical practice and further research.

Ethnicity and perinatal health outcomes

Main indicators of perinatal health outcomes are perinatal mortality and perinatal morbidity, including congenital disorders, a low birthweight as indicated by small-for-gestational-age (SGA), preterm birth (PTB) and a low Apgar score. We observed different prevalences of these perinatal health outcomes among the main ethnic groups in Amsterdam (i.e. the Dutch, Surinamese, Antillean, Ghanaian, Turkish and Moroccan group) (Figures 8.1-8.3). Compared to the Dutch newborns, newborns of all ethnic minority groups had on average a lower birthweight and a higher SGA risk. The prevalence of PTB was higher among the Surinamese, Antillean and Ghanaian group, but not among the Turkish and Moroccan group. When comparing the outcomes of first and second generation groups, different patterns were observed; while for the PTB prevalence a certain amount of convergence was noted between the second generation groups and the Dutch group, this was largely absent for the birthweights. The prevalence of a low Apgar score (score <7) and child loss (miscarriages and perinatal deaths included; abortions excluded) was highest among the Surinamese, Antillean and Ghanaian group. In contrast, no significant ethnic differences were found in the prevalence of congenital disorders; this prevalence may, however, be an underestimation in that child losses – which most likely include the most serious congenital disorders – were excluded from prevalence estimation. A similar phenomenon was probably responsible for the low prevalence of congenital disorders observed in the four largest cities in the Netherlands.1

While ethnic disparities in the prevalence of child loss are – without doubt – substantial, the consequences of ethnic disparities in perinatal morbidity rates are less clear. In general, SGA, a low Apgar score and – in particular – PTB have important consequences for a newborn’s future health and survival.2-7 However, when comparing populations, differences in mean birthweight and gestational age are not necessarily related to higher population mortality and morbidity rates; the entire population distribution of birthweight and gestational age may be ‘naturally’ shifted as a result of smaller stature (e.g. Surinam-Hindustani) or earlier fetal maturation (e.g. blacks).8-12 Nevertheless, we observed the highest rates of child loss and low Apgar scores among those ethnic groups (i.e. the Surinamese, Antillean and Ghanaian group) with the lowest birthweights and highest PTB prevalence. As the perinatal morbidity rates increased in the last decades, it becomes more and more important to explore its etiology; understanding the ethnic disparities in perinatal morbidity rates will be a huge step forward. This will – most likely – not only improve worldwide health but will also reduce societal and economical costs following adverse perinatal health outcomes.4,7,13-16
To reduce the ethnic disparities in perinatal health outcomes we have to understand how the broad concept of ethnicity is related to perinatal outcomes. Ethnicity in itself is a 'distal' factor that can only affect health through mediation of 'proximal' risk factors. Proximal risk factors (e.g. smoking, stress or nutrition) can directly affect health through pathophysiological mechanisms. We explored whether a set of conventional, mainly proximal risk factors mediated the observed association of ethnicity with birthweight and PTB risk. Lower birthweights among ethnic minority groups can be the result of either pathological growth restriction or a more 'natural' limited growth potential due to constitutional factors like maternal size, parity and maternal age. We concluded that, in our sample, an important part of the newborns of ethnic minority groups was constitutionally smaller due to ethnic differences in maternal height. In general, smaller mothers get smaller babies; this is, in fact, of evolutionary importance to secure safe vaginal deliveries. Paternal/fetal genome has therefore to be overruled by maternal constraint. Whether this has any negative consequences for future offspring health is, however, unknown. Another part of the newborns of ethnic minority groups was probably pathologically smaller, although higher prevalences of (working) stress and slightly higher prevalences of smoking and underweight among ethnic minority groups only appeared to be to a small extent responsible for the lower birthweights. With respect to ethnic disparities in PTB risk, we observed that ethnic differences in the prevalence of chronic hypertension, smoking, obesity and previous induced abortions partly explained the higher PTB risk among certain ethnic minority groups. At the end, compared to the Dutch group the Turkish and Moroccan group did not seem to have unfavorable perinatal health outcomes as their newborns were not at a higher PTB risk and were mainly constitutionally smaller due to smaller mothers (Figures 8.1 & 8.2). Similar findings have been reported in studies from Rotterdam (the Netherlands), Belgium, France and the USA. In contrast, the Surinamese, Antillean and Ghanaian group did seem to have unfavorable perinatal health outcomes, which could partly, but not fully, be explained by mediation of a set of conventional risk factors. Reducing this set of conventional risk factors will hence reduce, but not dissolve the higher perinatal morbidity rates among these groups. Studies in Rotterdam, France, the USA and the UK also reported the worst perinatal health outcomes among Afro-Caribbean and African women. While the Surinamese-Hindustani newborns possibly were constitutionally smaller, the newborns with an African ancestry probably had an excess risk explained by unexplored risk factors like maternal nutritional status and infections or, which we believe is more likely, by a cumulation of risk factors and/or (epi)genetic influences. Currently, research on (epi)genetic effects is rapidly growing, whereas research on cumulative risk profiles deserves more attention.

**Cumulation of risks**
In contrast to, for instance, the period of the Dutch famine, pregnant women are nowadays exposed to numerous 'small' risk factors. After years of research, it should be admitted that ethnic disparities in perinatal health outcomes are not likely to be explained by single effects of such small risk factors. Researchers therefore more and more emphasize to search for cumulative effects of multiple risk factors. Multiple pathophysiological processes probably cause much more
damage through interaction effects than a single harmful agent. We provided preliminary evidence for this cumulative risk hypothesis by presenting a cumulative effect of multiple risk factors (both proximal and distal risk factors) on PTB risk; the highest PTB risk was observed among the group of women with the highest number of risk factors. In addition, we observed a higher cumulation of risk factors among ethnic minority groups compared to the Dutch group, which appeared to be largely responsible for the ethnic disparities in PTB risk. These results seem promising, however, further research is necessary to support the preliminary findings and to develop an improved cumulative risk score with a higher predictive value. Only then it could be an effective tool for clinical practice for the purpose of screening pregnant women for their cumulative risk profile and addressing antenatal intervention programs to those women with the highest risk profile.

Recently, a new framework has been proposed that expands the cumulative risk hypothesis by stating that ethnic disparities in perinatal health outcomes not only result from differential cumulative risk profiles during pregnancy, but moreover from differential life course trajectories.17,35 This framework hypothesizes that a woman’s reproductive potential is largely set by fetal programming during her own fetal development.13,35 Subsequently, her reproductive potential is influenced by exposure to risk factors (e.g. infections, poor diets, chronic disease, stress) and protective factors (e.g. social support, coping) across the life course.17,35 Translating this life course approach to ethnic disparities in perinatal health outcomes, it is suggested that ethnic minority groups have a disadvantaged reproductive potential as a result of chronic exposure to poor socioeconomic conditions, infections, psychosocial stress and racism passed on across generations through fetal programming.34,35,40,41 Nonetheless, this life course framework is still in its early gestation and biological evidence from human studies is lacking.

Psychobiological pathways into ethnicity-related perinatal health outcomes

The potentially negative effects of maternal psychosocial stress on perinatal health outcomes increasingly get attention, especially in explaining ethnic disparities. In 2005, the March of Dimes (USA), for instance, recommended six research priorities for investigating the etiology of PTB; one of the priorities is to delineate the role of stress and accompanying psychobiological pathways in the risk for PTB and in ethnic disparities in PTB risk.15 Numerous research studies on the negative effects of maternal psychosocial stress on perinatal health outcomes have already been performed, however, results are very inconsistent.42-44 In contrast, research on psychobiological pathways into perinatal health outcomes is scarce.32,45 With the advantage of a large sample of pregnant women, we explored how maternal psychosocial well-being during pregnancy, as indicated by the amount of depressive symptoms, was related to major perinatal health outcomes and furthermore, how maternal cortisol concentration during pregnancy, as a biomarker of psychosocial stress, was related to fetal growth. We observed the highest prevalence of PTB, SGA, a low Apgar score and child loss among the group of women who reported high levels of depressive symptomatology during pregnancy. Only the prevalences of SGA and a low Apgar score remained, however, statistically significantly higher after correction for the effects of relevant covariates. Various indirect and/or direct pathways could be responsible for the higher risk of perinatal health problems among
women with high levels of depressive symptomatology during pregnancy. As we observed a higher smoking prevalence during pregnancy among women with psychosocial problems, these women could be indirectly at a higher risk for perinatal health problems through the toxic effects of cigarette smoking. Alternatively, these women could be directly at a higher risk through a psychobiological pathway involving altered concentrations of the hormone cortisol. Our data did, however, not seem to support such a pathway as we did not observe a statistically significant association of maternal cortisol concentration with both maternal psychosocial problems and offspring birthweight. The analysis was, however, hindered by methodological difficulties like the complex nature of the circadian cortisol rhythm.

Overall, we think the detrimental effects of maternal psychosocial stress during pregnancy on perinatal health outcomes are hard to elucidate because they depend on several intra- and interindividual factors. Normally, the human body responds to stress with the fight-or-flight response, i.e. complex feedback mechanisms of the cardiovascular, metabolic, immune and neuroendocrine system. Hereafter, the human body has to regain physiological stability or homeostasis through a mechanism called allostasis. This involves the regulation of biomarkers of stress, such as the corticotrophin-releasing hormone (CRH), cortisol, heart rate activity and blood pressure. In case of ‘allostatic load’, for example by chronic exposure to stress, the ‘set points’ of these biomarkers change in order to maintain physiological balance over time. This may result in pathophysiological effects like an increased blood pressure or heart rate or an abnormal neuroendocrinological response to stress. We hypothesize that pregnant women with allostatic load (also called ‘stress age’ or ‘weathering’) as a results of chronic stress exposure before and/or during pregnancy are at a higher risk for adverse perinatal health outcomes. In addition, the susceptibility of pregnant women to detrimental effects of psychosocial stress will also depend on their coping strategies, for instance the access to and utilization of social support. Future research is challenged by the search for those women who are most susceptible to detrimental effects of psychosocial stress during pregnancy on perinatal health outcomes; screening women for allostatic load by monitoring blood pressure, heart rate activity and the concentration of stress hormones (e.g. cortisol, CRH) seems a new and promising way to do so.

The theory of allostatic load is suspected to be highly relevant for women from ethnic minority groups. They are often exposed to chronic stress across the life course due to racism, low socioeconomic status and language and cultural differences. Within the ABCD cohort, ethnic minority groups reported higher levels of maternal psychosocial problems during pregnancy compared to the Dutch group. The prevalence of ‘depression’, for example, as operationalized by a score of 16 or higher on the Center for Epidemiologic Studies Depression Scale (CES-D), was respectively 44%, 41%, 55%, 42%, and 34% for the Surinamese, Antillean, Turkish, Moroccan and Ghanaian group compared to 22% for the Dutch group. And while 0.5% of the Dutch group reported exposure to physical and/or sexual violence during pregnancy, this ranged from 0.6% to 3.1% among the ethnic minority groups. In additional analyses, we explored whether the higher prevalence of psychosocial stress during pregnancy among ethnic minority groups actually was responsible for their higher prevalence of adverse perinatal outcomes; we therefore expanded...
the risk models for low birthweight and PTB with maternal psychosocial problems (depressive symptoms, pregnancy-related anxiety, parenting stress, work stress and physical/sexual violence). The results are shown in Figures 8.1 and 8.2, represented in the third bar for each ethnic group. In contrast to what expected, ethnic disparities in birthweight and PTB risk could not be explained by ethnic differences in maternal psychosocial problems. In theory, the explored associations might be more complex in that psychosocial stress may interact with ethnic background in affecting perinatal health outcomes. Such an interaction effect could potentially be attributed to higher allostatic load among ethnic minority groups and/or higher vascular activity and reactivity to stress among blacks.40,51 This needs, however, to be elucidated in future research.

Psychobiological pathways into infant health outcomes

Beyond the importance to elucidate psychobiological pathways that connect maternal psychosocial well-being during pregnancy with perinatal health outcomes, it is of growing importance to elucidate the psychobiological pathways that connect maternal health during pregnancy with infant psychosocial well-being. In fact, some risk factors during pregnancy may not affect fetal growth or the time of parturition, meanwhile damaging certain developing physiological systems. A poorly understood indicator of infant psychosocial stress is excessive infant crying or infant colic. While excessive infant crying can be partly attributed to postnatal factors like parental caring or milk allergy,52 further etiology may originate in early fetal development. Several maternal risk factors during pregnancy, including maternal psychosocial stress and smoking, have been linked to excessive infant crying.53,54 A potential link with the nutritional status of the mother during pregnancy is yet missing, while it is known that nutrients are essential for fetal neurodevelopment.55,56 We hypothesized that maternal folate and vitamin B-12 status during pregnancy could be related to infant crying behavior. Our data confirmed this hypothesis for vitamin B-12 but not for folate. The psychobiological pathway explaining the observed association most likely involves the fetal development of the circadian sleep-wake rhythm. The development of this rhythm depends on the hormone melatonin; melatonin synthesis, in turn, depends – among others – on vitamin B-12.57 Excessive infant crying in the first months of life could be a symptom of an immature sleep-wake rhythm.58,59 These data provide first evidence for an early nutritional origin in excessive infant crying. The results, however, require confirmation. Further research should explore the hypothesized psychobiological pathway, the threshold level at which maternal vitamin B-12 status becomes alarmingly low, and the possible moderating role of maternal psychosocial problems. If confirmed, this could have important implications for (i) clinical practice, in that screening and treating pregnant women for vitamin B-12 deficiency will decrease the number of excessively crying infants, and (ii) for public health, in that the psychosocial well-being of infants and their parents will improve.
Figure 8.1 Ethnic differences in term birthweight (BW).
Model 1: Crude BW differences (g, 95% CI) with the Dutch group as the reference group; Model 2: BW differences, adjusted for all relevant covariates (see Chapter 2); Model 3: BW differences, additionally adjusted for maternal psychosocial problems during pregnancy.
Figure 8.2 Ethnic differences in PTB risk.
Model 1: Crude PTB risk (OR, 95% CI) with the Dutch group as the reference group; Model 2: PTB risk, adjusted for all relevant covariates (see Chapter 3); Model 3: PTB risk, additionally adjusted for maternal psychosocial problems during pregnancy.
Figure 8.3 Ethnic differences in the risk (OR, 95% CI) for a low Apgar score, child loss and congenital disorders, with the Dutch group as the reference group.
Methodological considerations

The research questions of this thesis were examined within the context of the Amsterdam Born Children and their Development (ABCD) study. The ABCD study is a large prospective birth cohort study aimed at exploring the association between (ethnic differences in) maternal risk factors during pregnancy and (ethnic disparities in) perinatal and infant health outcomes. In this paragraph, we will discuss some methodological issues regarding the ABCD study design and sample and the measurement of major variables mentioned in this thesis.

ABCD study: design and sample

One of the main strengths of the ABCD study is the large unselected community-based sample. During the inclusion period, all pregnant women in Amsterdam were approached by participating obstetric caregivers at their first regular prenatal visit. Because women were approached by a reliable source, the response rate was high (67%) and the sample diverse with respect to socioeconomic and ethnic background and health status. The actual participation was still somewhat selective, with a higher participation rate among Western groups, especially for the ABCD biomarker study (collection of an extra blood sample for research purposes). Despite the selective participation, selection bias appeared to be acceptably low as the association between a number of conventional risk factors and perinatal health outcomes was similar for respondents and non-respondents. Hence we assume that the observed associations reported in this thesis will be hardly influenced by selective participation.

Another strength of the ABCD study is the collection of a comprehensive set of maternal risk factors through maternal blood samples and questionnaire data. The maternal risk factors were measured around the end of the first trimester and beginning of the second trimester of pregnancy. This period of early gestation is suggested to be a particular sensitive period for maternal-placental-fetal pathophysiology and fetal programming because of the rapid organ development. Some risk factors, for instance cigarette smoking, infections or acute severe stress, however, might have non-programming effects on fetal growth and parturition in late pregnancy; unmeasured levels of such risk factors in late pregnancy could have influenced our risk models for adverse perinatal health outcomes.

Ethnicity

Ethnicity was based on the self-reported country of birth of the pregnant woman and her mother – to distinguish between first and second generation – and categorized into the main ethnic groups in Amsterdam: Dutch, Surinamese, Antillean/Aruban, Ghanaian, Turkish, Moroccan and other non-Dutch (Western and non-Western) group. The ABCD study sample was representative for the ethnic distribution in Amsterdam. The use of the variable ethnicity in epidemiological research is highly debated, but nonetheless very useful when searching for explanations of health disparities. Classification by country of birth is widely used to define ethnic groups for it is an objective and stable measure. In addition, it often reflects both racial ancestry and cultural habits.
It could, however, not differentiate between ethnic subgroups, for example Surinamese-Creole and Surinamese-Hindustani groups.\textsuperscript{63,66} For this purpose, self-identification of ethnicity would be more useful. Within the ABCD study, an additional question on self-identification provided data on ethnic subgroups. Nevertheless, we preferred to base ethnicity mainly on country of birth of the pregnant woman and her mother rather than on self-identification, because the latest measure is not stable over time and does not reflect racial ancestry,\textsuperscript{63,66} which we think may be important in explaining ethnic disparities in perinatal health outcomes. The operationalisation of ethnicity in future research among next generations will yet be more complicated as country of birth will then not be a reflection anymore of racial ancestry and cultural background.

**Measurement of maternal psychosocial health**

Maternal psychosocial health during pregnancy was measured in the pregnancy-questionnaire through several well-validated psychosocial scales: the Center for Epidemiologic Studies Depression scale (CES-D)\textsuperscript{67} measured depressive symptomatology, the state-scale of the State-Trait Anxiety Inventory (STAI)\textsuperscript{68} measured anxiety, the Pregnancy Related Anxiety Questionnaire - Revised version (PRAQ-R)\textsuperscript{69,70} measured pregnancy-related anxiety, the Work Experience and Appreciation Questionnaire (VBBA)\textsuperscript{71,72} measured job strain and finally, the frequency scale of the Parenting Daily Hassles (PDH)\textsuperscript{73} measured parenting stress. Additionally, women were retrospectively asked in the baby-questionnaire whether they were exposed to physical and/or sexual violence during pregnancy. Cronbach's alphas for the psychosocial scales ranged from 0.81 to 0.94. Though the scales have good internal consistency, are well validated and are more or less used in previous research, they have several methodological limitations. First, the CES-D and STAI can not be used to diagnose respectively a depressive or anxiety disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Though it might be possible that there is a dose-response relationship with mental disorders having a more negative impact on perinatal health outcomes than subclinical levels of depression or anxiety, this is not yet proved.\textsuperscript{42,74} Second, it is questionable whether certain psychosocial scales are as suitable in a pregnant population as in the general population, because of the risk for somatic confounding. Certain symptoms of pregnancy are, for example, similar to depressive symptoms (e.g. tiredness, loss of appetite).\textsuperscript{75} Restricting our analysis to non-somatic symptoms did, however, not improve the predictive capacity of the CES-D scale for perinatal health outcomes, which supported previous research.\textsuperscript{76} Third, it is not clear whether psychosocial scales have the same validity across ethnic groups, because some ethnic groups tend to somatize psychosocial stress much more. The few studies which explored this issue observed good validity and internal consistency of psychometric scales across ethnic groups, but suggested that cut-off points for detecting psychiatric disorders could be different.\textsuperscript{77-80} Further research on the validity and diagnostic thresholds of psychosocial scales across various subpopulations is necessary for the purpose of epidemiological research as well as for screening purposes in clinical practice.

One of the best ways of assessing the pathophysiological effects of maternal psychosocial stress during pregnancy on fetal health is by assessing biomarkers of stress. A well-accepted
Biomarker of stress is the hormone cortisol, which is released by the hypothalamic-pituitary-adrenal (HPA) axis in response to a stressor. As part of the ABCD biomarker study, we measured total cortisol concentration in serum in a large sample of more than 4000 pregnant women. Nonetheless, the use of cortisol in epidemiological research involves some methodological difficulties. First, general cortisol secretion is characterized by a circadian rhythm with peak levels shortly after awakening and a more or less declining pattern thereafter. It is hypothesized that the cortisol awakening response (CAR) reflects a different HPA-axis functioning than the cortisol secretion throughout the rest of the day. The CAR is suspected to be a good marker of psychosocial stress. Whether an altered CAR of the mother also has the most detrimental effects on fetal health is, however, unclear; so far, preliminary evidence is only provided by animal research. With only one cortisol measurement for each pregnant woman, we were not able to make a statement on the specific relationship of various parts of the diurnal cortisol rhythm with fetal health. We did, however, observe explicitly lower offspring birthweights among mothers with high versus low cortisol concentrations in the morning compared to other time points across the day. Second, it is hypothesized that free cortisol concentration is a better marker of potential pathophysiological effects than total cortisol concentration. Preliminary evidence suggests that exposure to stress decreases corticotrophin-binding globulin (CBG) concentration, resulting in a different ratio of total vs. free cortisol. If confirmed, free cortisol concentration should preferable be used in exploring the pathophysiological effects of stress on fetal health. In conclusion, our cortisol measurement suffered from serious limitations leaving the lack of an observed association between maternal cortisol concentration and both maternal psychosocial stress and offspring birthweight open to doubt. Much need to be done to reveal the best way to operationalize maternal cortisol concentration in exploring its pathophysiological effects on perinatal health outcomes. Until then, screening pregnant women for altered cortisol concentrations will not be effective.

**Measurement of perinatal and infant health outcomes**

Data on gestational age and offspring birthweight were highly available from the Youth Health Care registration at the Public Health Service in Amsterdam. An 80% linkage (higher for Western groups) with the Dutch Perinatal Registration (PRN) provided a second source of information on perinatal health outcomes. To define whether neonates were SGA, reference data from the PRN, matched on the period of deliveries within the ABCD cohort, were used. Although the SGA categorization accounted for the non-pathological effects of fetal gender and parity on birthweight, it did not account for the effects of maternal height. As a result, newborns of very small mothers (especially seen among some ethnic minority groups) could have been wrongly categorized as SGA. Gestational age was mostly based on ultrasound measurements; when unavailable (<10%), gestational age was based on the first day of the last menstrual period (calculation by obstetric care provider). Perinatal outcome data were incomplete (particularly for non-Western groups) for the type of preterm delivery (spontaneous vs. iatrogenic) and Apgar scores, because these data were only available from the PRN. Data on fetal/infant mortality was most likely incomplete for miscarriages.
The amount of infant crying was measured in the baby-questionnaire (±3 months after birth) with the question: ‘How many hours per day (24 hours) on average did your baby cry in the past week?’ We defined excessive infant crying as crying on average ≥3 hours per day in the past week. Worldwide, no consensus has been reached for the definition of excessive infant crying, also called infant colic. Used criteria for excessive crying range from crying >3 hours/day on >3 days/week for >3 weeks to an unquantified ‘cries a lot’. Depending on the criteria used, different groups of infants are included. This is a problem for the comparison of research as well as for clinical practice. The reason for infants to cry excessively has different etiologies that are hard to distinguish. The association we observed between low maternal vitamin B-12 status during pregnancy and excessive infant crying may therefore be different depending on the homogeneity of cases. In future research, prospective measurements with diaries and audiotape recordings rather than retrospective questionnaires should preferably be used to diagnose various types of excessive infant crying, however, such measurements are difficult to achieve in large-scale epidemiological studies.

**Implications for interventions**

The period of pregnancy is one of the best opportunities for health interventions. Pregnant women are usually more willing to make an effort for healthy behaviors in order to restrict the possible health risks for their unborn child. In high income countries, antenatal educational programs are largely attended by pregnant women. There is, however, a huge gap in our knowledge about the efficacy of these programs. Though pregnant women evaluate antenatal programs as highly valuable and as an important source of information on risk behaviors, it is unclear whether there is an actual benefit for the health of the mother and her child. The efficacy of antenatal programs should hence be better evaluated in order to improve maternal and child health.

Important risk factors for perinatal and infant health outcomes that are amenable for intervention are maternal smoking, obesity, nutritional status and psychosocial stress. First, the toxic effects of maternal smoking during pregnancy are believed to be one of the most harmful effects on fetal development. Although most women seem to be aware of the fetal health risks from smoking, 38% of the pre-pregnancy smokers in our sample continued to smoke during pregnancy, resulting in a smoking prevalence of 9% during pregnancy. As the detrimental effects of smoking can immediately be stopped by quitting smoking, effective smoking cessation programs for pregnant women are crucial. Smoking cessation programs like cognitive-behavioral and nicotine replacement therapy have been shown to reduce smoking and to improve perinatal health outcomes. In contrast to smoking, immediate intervention effects are more difficult to achieve for obese pregnant women. As the risk for obesity often accumulates over the life course as a result of multiple determinants (e.g. rapid weight gain during infancy, poor nutritional habits, sedentary lifestyle), comprehensive interventions across the life course are necessary to ensure a preconceptional healthy body weight. Nevertheless, it will still be useful to give advice on healthy nutrition and physical activity during
antenatal educational programs. In fact, nutritional advice on, for example, folic acid and vitamin B-12 intake can have immediate positive effects on fetal development.

The rising prevalence of psychosocial problems is becoming a public health problem. Obstetric caregivers should be aware of the impact of this problem on maternal and fetal health. The negative consequences of maternal psychosocial stress during pregnancy on fetal development more and more emerge, stressing the need to develop and implement intervention programs for pregnant women with psychosocial stress. Screening women for psychosocial stress should be part of routine antenatal care, accompanied by well-planned treatment referral preferably at the same site as the obstetrical provider. Promising treatments for psychosocial stress include cognitive-behavioral therapy, relaxation techniques and social support. For mental disorders like depression, pharmacologic treatments are proved to be efficacious, however, many pregnant women are reluctant to use medication because of concerns about the impact on the fetus. There is yet a striking need for more research on efficacious and safe (non)pharmacologic interventions for pregnant women with psychosocial problems.

An important shortcoming of many antenatal health promotion programs is the focus on single rather than multiple risk behaviors, while the majority of pregnant women face more than one risk factor simultaneously. Moreover, risk behaviors are often highly connected; stressed women, for example, tend to smoke more often and also show poorer nutritional habits. Proximal risk behaviors like stress, smoking and nutritional habits often share the same distal risk factors like financial problems or lack of social support. Comprehensive antenatal intervention programs that cover not only important proximal risk behaviors but also distal factors like economic conditions or social environment will therefore be most effective to reduce adverse perinatal health outcomes. The Dutch ‘VoorZorg’ program, in which low-educated teenage pregnant women receive intensive support during and after pregnancy, is a good example of a perinatal education program that covers both proximal and distal risk factors.

Another shortcoming of antenatal programs is the limited reach of ethnic minority groups, while those groups are most in need for intervention programs because of their high-risk profile. They often have a high cumulation of both distal and proximal risk factors, and furthermore, they tend to start late with antenatal care visits to obstetric care providers. To reduce ethnic disparities in perinatal health outcomes, easy accessible antenatal programs are needed that are adjusted to specific ethnic groups to account for cultural and language differences. It is, for example, observed that folic acid use before and during pregnancy is much lower among non-Dutch-speaking women. Furthermore, cultural-specific beliefs and norms about, for instance, smoking, nutrition, physical activity and emotional problems are important determinants of risk behaviors in certain ethnic groups. An example of an ethnic-specific antenatal intervention program is the Dutch program ‘Blije Moeders, Blije Babies’ (BMBB) which focused on Turkish pregnant women. BMBB covered multiple risk factors including maternal smoking behavior and depressive feelings. Although the BMBB program did not seem to have an effect on smoking prevalence while only a small effect on the level of depressive feelings, the program was very successful in reaching an underserved minority group through Turkish community health workers. While in the next
generations language problems most likely will disappear, it will depend on the future level of acculturation whether cultural-specific beliefs and norms should be accounted for in antenatal health promotion programs.

Ideally, prevention of (ethnic disparities in) adverse perinatal health outcomes starts preconceptionally rather than at the first prenatal visit when it is largely too late. In the Netherlands, the Erasmus Medical Center in Rotterdam was one of the firsts to start with a pilot study on preconceptional counseling. Couples planning to be pregnant were screened and educated on modifiable risk factors. After three months, significant improvements were observed on the prevalence of obesity, folic acid use, alcohol use and physical activity, but not on the use of cigarettes and drugs. To reduce addictive behaviors, a more intensive approach will probably be needed. Nonetheless, the pilot on preconceptional counseling seems promising and should be further developed.

Final conclusion

The main aims of this thesis were to explore and explain the ethnic disparities in perinatal health outcomes in Amsterdam and furthermore, to explore the psychobiological pathways into perinatal and infant health outcomes. Based on observations within the ABCD cohort and a reflection on these observations, the following concluding points could be drawn:

(1) 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.

(2) 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.

(3) 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.
References


