DRUG DEPENDENCE IN PREGNANCY
- AN AUDIT OF THE MULTIDISCIPLINARY APPROACH IN ROTTERDAM 1983-1992 -

AFHANKELIJKHEID VAN DRUGS IN DE ZWANGERSCHAP
- EEN TOETSING VAN DE MULTIDISCIPLINAIRE BENADERING IN ROTTERDAM 1983-1992 -

Drug dependence in pregnancy / Monica Pop-Purceleanu
Proefschrift Rotterdam
ISBN 90-9007995-5
Keywords: Drugs, pregnancy, antenatal care, fetal growth, methadone

omslag: **Keith Haring** (1958-1990) «Birth» Image / sept. 1986

DRUG DEPENDENCE IN PREGNANCY

- AN AUDIT OF THE MULTIDISCIPLINARY APPROACH IN ROTTERDAM 1983-1992 -

AFHANKELIJKHEID VAN DRUGS IN DE ZWANGERSCHAP

- EEN TOETSING VAN DE MULTIDISCIPLINAIRE BENADERING IN ROTTERDAM 1983-1992 -

PROEFSCHRIFT
TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
AAN DE ERASMUS UNIVERSITEIT ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF.DR. P.W.C. AKKERMANS M.A.
EN VOLGENS BESLUIT VAN HET COLLEGE VOOR PROMOTIES
DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN OP
WOENSDAG 8 FEBRUARI 1995 OM 15.45 UUR

DOOR

MONICA POP-PURCELEANU

GEBOREN TE CLUJ

Promotiecommissie

Promotor	Prof.dr. H.C.S. Wallenburg
Overige leden	Prof.dr. I.D. de Beaufort Prof.dr. W.J. Schudel Prof.dr. H.K.A. Visser

To Gheorghe, Stefan and Carmen
to my parents

CONTENTS

Chapter 1

INTRODUCTION

The obstetric and pediatric complications of pregnancies associated with abuse of psychoactive substances, usually denoted as "drugs", have been receiving increasing attention in the medical literature, especially after 1956 when M.J.Goodfriend published a review of case histories recorded in the literature since 1892. Many of his conclusions, such as "narcotic addiction with abstinence symptoms is a distinct clinical entity in the newborn" have remained valid until today[82]. The seventies brought the first large American studies about addiction in pregnancy, its management and perinatal outcome[19,65,103,147,150,155,159,190,192,193,212,213,214,217]. Between 1970 and 1980 family and maternity care programs were established in the United States, in an attempt to solve the overwhelming problems of drug abuse and dependence in pregnant women[41,65,89,150,156,193]. In the same period substance abuse became increasingly frequent in The Netherlands, and the first Dutch reports appeared about pregnancies complicated by opiate abuse[96,116,185]. Also the Dutch health, legal and social care providers became confronted with the complex problem of drug addiction in pregnancy.

Descriptions of American policies[89,150,193] in particular the program instituted in Philadelphia[41,65], their outline of treatment, and the discussion generated by their results, were used to develop a preliminary model for the Dutch approach. Amsterdam was the first city in the Netherlands that initiated a medical and social network for children of drug dependent parents[96,185]. Although substantial support was provided for pregnant addicts, neither the American nor the Amsterdam approach succeeded in establishing a standardized multidisciplinary program of obstetric and pediatric care, centralized for a whole region or city.

Following Amsterdam, also Rotterdam was confronted in the beginning of the eighties with an alarming increase in the number of pregnant addicts. In Rotterdam these problems, encountered by physicians and social workers as well as by municipal and legal institutions, led to the development and institution of a multidisciplinary approach for drug abusing

pregnant women. In 1982 it was agreed among all institutions involved to centralize the obstetric care for these women in the city of Rotterdam in the Department of Obstetrics and Gynecology of the AZR-Dijkzigt, based on the premises that centralization would improve care, and that it would facilitate the coordination of medical and psychosocial approaches within the network. The aim of the multidisciplinary team was to provide health care and to support the drug dependent woman facing a life crisis created by pregnancy. The physiologic and psychologic effects of substance abuse, low-self esteem, fear of being identified as unable to take care of the baby, past or present traumatic experiences, environment and activities related to drug supply were recognized as strong barriers for drug dependent pregnant women to gaining access to antenatal care.

The centralized, integrated multidisciplinary approach to the care of drug abusing pregnant women was introduced in 1983. The obstetric care was based on the following principles:

1. Pregnancies in drug abusing women are at high risk. Prevention and/or reduction of obstetric and medical risks constitute priorities in the antenatal care for these patients.
2. Family planning, contraception and basic health care education have an important place in the antenatal and postpartum care of drug abusing patients.
3. Specialized treatment should be available for all substance dependent pregnant women seeking antenatal care.
4. The obstetric protocol for drug abusing patients should be combined with psychosocial support.
5. Encouragement of mother/infant bonding should start antenatally and be continued after delivery.
6. Follow-up is required to assess the long term consequences of mothers' drug abuse upon their offspring and to warrant a safe environment for the infant.

Within this framework, the obstetric protocol aimed at early referral of drug dependent pregnant women for antenatal care, standard investigations for the diagnosis of diseases known to have a high prevalence in this population, a clearly outlined approach to delivery and the postpartum period, optimal communication and collaboration with the neonatology department, proper ante and postpartum medical education including family planning and basic child care. The obstetric approach was closely associated with specialized treatment for drug dependency and intensive social support through social and child protective

institutions. The obstetric protocol warranted a systematic approach and served as a guideline in every day practice but it never overran the clinical setting and the relationship between patient/client and care provider.

The integrated multidisciplinary approach represented a milestone in the management of drug dependent pregnant women in Rotterdam and it has remained largely unchanged during 10 years. It was considered that, after a decade, the time had come to audit this approach in its structure, process and outcome. According to the definition given by the British Government in their White Paper Working for Patients[127], a medical audit is a systematic, critical analysis of the quality of medical care including:

* the quality of life and outcome for the patient
* the procedures used for diagnosis and treatment
* the use of resources

with the objective of improving the care given to patients. Fig. 1.1 presents schematically the phases of an audit study.

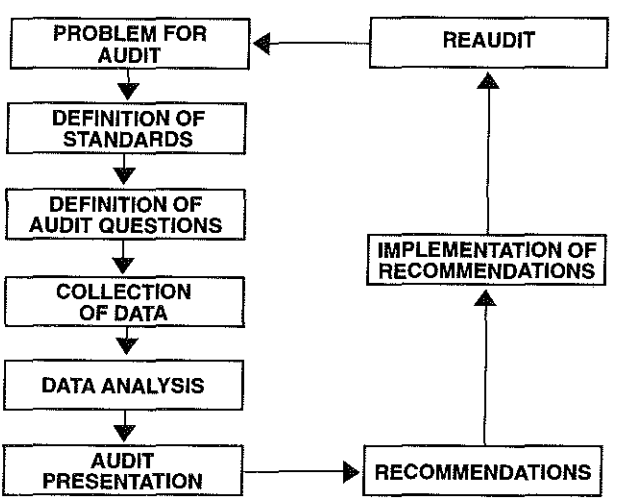


Fig. 1.1 The audit cycle (modified after 127)

An audit study of the multidisciplinary obstetric approach to the care of drug dependent pregnant women should be a source of progress along an axis of improving health care. With this aim, the audit study reported in this thesis was designed to analyze and discuss the structure, execution and results of the integrated obstetric approach carried out in Rotterdam in the period 1983-1992. The audit was designed as a case-controlled study, including a population of non-drug dependent pregnant women, to provide answers to the following questions:

1. What are the obstetric results obtained with the integrated multidisciplinary approach in Rotterdam in drug dependent pregnant women compared with those of a control population of non-drug dependent pregnant women ?
2. Are there improvements or changes in the pregnancy outcome of drug dependent women in the course of 10 years of consequent application of the multidisciplinary protocol ?
3. What are the critical points of this protocol and which measures could be taken to improve its design and implementation ?

Chapter 2 presents the design of the obstetric protocol for drug dependent pregnant women, discussed on the basis of the knowledge that determined its development in 1982, and the methodology of the study. In chapter 3 the characteristics of the study population and the control groups will be presented and discussed. The obstetric results concerning the enrollment in the antenatal care and the course of pregnancy will be presented and discussed in chapter 4. Results concerning the delivery and the newborn are the subject of the 5th chapter. The thesis ends with chapter 6, in which a general discussion of the study is presented, with recommendations for improvement of care.

Chapter 2

DESIGN OF THE STUDY

This chapter presents the selection criteria for all patients included in the study, the methods of data collection, and of statistical analysis, and the definitions of all variables used. The general antenatal care program and the multidisciplinary approach for drug-dependent pregnant women are described in detail. The obstetric approach is discussed in the light of the medical knowledge at the time of its introduction in 1983. Changes in the obstetric protocol, due to medical progress after 1983, are also presented.

2.1 Selection of subjects

Study group

A total number of 170 women, delivered in the Department of Obstetrics and Gynecology of the University Hospital Rotterdam between 1983 and 1992, admitted to be substance dependent and tested positive for opiates and/or cocaine, used in different amounts, frequency, duration, associations and routes of administration. Opiate dependence was the determinant for enrollment in the study group. Polydrug users were included in the study if they were opiate dependent and used in addition to opiates other drugs (cocaine, amphetamines, benzodiazepines).

A drug dependent woman could give birth one or more times during the ten years period of the study. The group of 170 hard-drug dependent patients were delivered of 187 infants in the Department of Obstetrics and Gynecology of the University Hospital Rotterdam. Twin pregnancies were excluded from the study. Each pregnancy followed by a delivery in the University Hospital Rotterdam was regarded as a separate entity, reason why the study group consists of 187 obstetric cases. The majority of the women attended the antenatal care program for substance dependent patients, but the study population also includes drug dependent women who withdrew from antenatal care and were admitted in labor. Their drug use was certified by self-report, positive urinalysis on drug metabolites for mother and infant, and development of a neonatal withdrawal syndrome. Drug

dependent women under antenatal care in the University Hospital Rotterdam but delivered in another institution were not included in the study.

Control group

Course and outcome of pregnancy in the 187 cases of drug dependence were compared with those in a control group of women without any evidence of drug abuse or dependence. The control women were selected with the use of the registry of deliveries in a blinded fashion, i.e without access to any obstetric information about the patients and their pregnancies. Following the delivery of a hard-drug dependent woman, the first delivery registered of a woman with the same parity, the same age (+/- 1 year), a singleton pregnancy and antenatal care in the outpatient clinic of the University Hospital Rotterdam was chosen as the case control. Drug screening by urinalysis was only performed in case of suspicion, after informed consent had been obtained. No women who were ever suspected of drug abuse or who refused drug screening were included in the control group. All pregnant subjects, drug dependent and controls, were matched case by case. Drug dependent women who delivered more than once during the study period were registered as new cases and were matched again with a new control case. A woman could not serve more than once as a control for a drug dependent patient.

After drug dependent patients and case-controls were matched, their medical records were obtained from the Medical Registry of the University Hospital, and reviewed. A data-base computer program was used to store the information from each patient in coded form. All information was coded by one investigator, the author of this thesis; no other person had access to the data, and all personal data were destroyed after codification.

The collected data was arranged according to a scheme that covered an array of 95 variables characterizing the course of pregnancy, labor and puerperium.

No informed consent was obtained from the individuals participating in this observational study for the following reasons:

1. The nature of the study group makes it practically impossible to obtain current addresses in the majority of cases.
2. In individuals who have become clean, inquiries could remind them and their environment of a past that they would prefer to remain buried.
3. The study serves a general interest and cannot be performed without the necessary information.

4. Access to the personal files was limited to the single investigator, and after codification all personal data were destroyed. For that reason privacy was guaranteed.

2.2 Definition of variables

Psychoactive substance abuse and dependence

Substance. Represented by chemicals, alcohol, drugs, non-drug stuffs.

Drug. This term defines a pharmacologically active substance that has distinctive chemical effects on the brain. Although in this context alcohol is also a drug[138], the term drug will be used in this study only for opiates and/or cocaine. Amphetamines and benzodiazepines will always be indicated by their generic name. When a special condition appears that is related to a specific substance, the substance will be reported with its pharmacologic name (for example: abruptio placentae related to cocaine). Alcohol and tabacco will be mentioned separately when necessary. In this text, "drug use" is a descriptive term, indicating the consumption of a psychoactive substance without defining a behavioral pattern of use.

Substance abuse. Characterized by a maladaptive pattern of use[9]. The individual recognizes the existence of the social, psychological, or occupational problems caused or exacerbated by the use of the substance, but despite this continues using the substance. All other criteria for psychoactive substance dependence (e.g: withdrawal symptoms, relapse etc.) are not applicable to these patients. (Table 2.1)

Table 2.1 *Diagnostic criteria for psychoactive substance abuse*[9]

A. A maladaptive pattern of psychoactive substance use indicated by at least one of the following:

   (1) continued use despite kwnowledge of having a persistent or recurrent social, occupational, psychological, or physical problem that is caused or exacerbated by use of the psychoactive substance

   (2) recurrent use in situations in which use is physically hazardous (e.g., driving while intoxicated)

B. Some symptoms of the disturbance have persisted for at least one month, or have occurred repeatedly over a longer period of time

C. Never met the criteria for Psychoactive Substance Dependence for this substance

Substance dependence. Table 2.2 presents the diagnostic criteria for psychoactive substance dependence as defined by DSM-III R[9].

Table 2.2 *Diagnostic criteria for psychoactive substance dependence[9].*

A. At least three of the following:

(1) substance often taken in larger amounts or over a longer period than the person intended
(2) persistent desire or one or more unsuccessful efforts to cut down or control substance use
(3) a great deal of time spent in activities necessary to get the substance (e.g., theft), taking the substance (e.g., chain smoking), or recovering from its effects
(4) frequent intoxification or withdrawal symptoms when expected to fulfill major role obligations at work, school, or home (e.g., does not go to work because hung over, goes to school or work "high" intoxicated while taking care of his or her children), or when substance use is physically hazardous (e.g., drives when intoxicated)
(5) important social, occupational, or recreational activities given up or reduced because of substance use
(6) continued substance use despite knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by the use of the substance (e.g., keeps using heroin despite family arguments about it, cocaine-induced depression, or having an ulcer made worse by drinking)
(7) marked tolerance: need for markedly increased amounts of the substance (i.e., at least a 50% increase) in order to achieve intoxination or desired effect, or markedly diminished effect with continued use of the same amount

Note: The following items may not apply to cannabis, hallucinogens, or phencyclidine (PCP):

(8) characteristic withdrawal symptoms (see specific withdrawal syndromes under Psychoactive Substance-induced Organic Mental Disorders)
(9) substance often taken to relieve or avoid withdrawal symptoms

B. Some symptoms of the disturbance have persisted for at least one month, or have occurred repeatedly over a longer period of time

Criteria for Severity of Psychoactive Substance Dependence

Mild: Few, if any, symptoms in excess of those required to make the diagnosis, and the symptoms result in no more than mild impairment in occupational functioning or in usual social activities or relationships with others
Moderate: Symptoms or functional impairment between "mild" and "severe"
Severe: Many symptoms in excess of those required to make the diagnosis, and the symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others[1]
In Partial Remission: During the past six months, some use of the substance and some symptoms of dependence
In Full Remission: During the past six months, either no use of the substance, or use of the substance and no symptoms of dependence

[1] Because of the availability of cigarettes and no other nicotine-containing substances and the absence of a clinically significant nicotine intoxication syndrome, impairment in occupational or social functioning is not necessary for a rating of severe Nicotine Dependence

Substance dependence is characterized by impaired control over the use of a psychoactive substance, despite its adverse consequences. The preoccupation to get the substance dominates the life of the patient and attempts to cut off the use of the substance have failed. A marked tolerance for the substance develops, which increases the daily need in order to achieve the desired effect. Characteristic withdrawal symptoms are relieved or avoided by regular use of the substance. The disturbance has persisted for at least one month, or has occurred repeatedly over a longer period of time.

At least three of the diagnostic criteria for psychoactive substance dependence according to the DSM-III-R classification for psychoactive substance disorders had to be fulfilled to include a patient in the category of drug dependence (Table 2.2). The term dependence used in this thesis indicates only that the study patients fulfilled the diagnostic criteria of DSM-III-R to be included in the substance dependence syndrome. The criteria included in the DSM-III-R classification define both dependence and addiction. We agree with Miller[138] that, in a strict interpretation, dependence is a pharmacological term that does not define addiction. The drug using pregnant women enrolled in this study showed a pattern of drug use characterized by preoccupation with the acquisition of the drug (opiate and/or cocaine), compulsive use of the drug, a history of relapse in the use of the drug, and impaired functioning due to drug use. In such cases the term addiction seems to be justified and it will be used interchangeably with the term dependence defined by the international classification.

The patient

Age. The age of the patient on the day of delivery, rounded off to half a year.

Nulligravida. A woman who is not and has never been pregnant, irrespective of the type or duration of pregnancy.

Primigravida. A woman who is or has been pregnant once, irrespective of the type or duration of pregnancy.

Multigravida. A woman who has been pregnant more than once, irrespective of pregnancy outcome.

Nullipara. A woman who has never completed a pregnancy beyond 16 weeks, irrespective of the number of pregnancies and the kind of abortions (spontaneous or elective).

Primipara. A woman who has been delivered once of a fetus or fetuses after completing

at least 16 weeks of pregnancy.

Multipara. A woman who has had more than one delivery after 16 completed weeks of pregnancy.

Duration of pregnancy. The expected date of confinement is calculated at 280 days or 40 weeks, from the first day of the last normal menstrual period. The duration of pregnancy is expressed in completed weeks of gestation.

Socioeconomic variables

Accomodation. The accomodation was defined as good when a visit by the social worker had documented the availability of water, gas, electricity, heating system, shower, stove and essential pieces of furniture (bed, table, chairs, chests). The accomodation was considered bad when two or more of the criteria named above, in particular the water and gas/electricity system, were missing. The woman was considered homeless when she did not have any accomodation and was living on the street.

Resources. The following sources of income were defined for drug dependent pregnant women: earnings through legal employment, unemployed woman with employed partner, unemployment benefit, regular financial support from parents, prostitution (defined as trading sex for drugs and/or money on a regular basis) and no known source of income.

Situation of previous children. According to the person(s) or institution in charge to rear the infant(s), the following situations were recorded:

a. Child(ren) living with the mother (alone or with a partner)
b. Child(ren) living with the father
c. Child(ren) living with grandparents (recognized as legal guardians of the child)
d. Child(ren) in foster care because mother lost custody over her offspring or renounced parenthood
e. Child(ren) in foster care while mother had not legally lost her custody

Complications of pregnancy

Chronic hypertension. Hypertension with a diastolic blood pressure of 90 mm Hg or more that antedates pregnancy or is diagnosed before 20 weeks of pregnancy.

Pregnancy-induced hypertension. A diastolic blood pressure of 90 mm Hg or more, in at

least two successive measurements with an interval of at least 6 hours, without proteinuria, developing after 20 completed weeks of gestation in a previously normotensive woman.

Preeclampsia. A diastolic blood pressure of 90 mm Hg or more, with a protein excretion of at least 300 mg/24 hours urine.

Eclampsia. Preeclampsia accompanied by seizures during pregnancy, labor or in the first 48 hours postpartum.

HELLP syndrome. Preeclampsia accompanied by hemolysis (peripheral blood smear), elevated liver enzymes (ASAT and ALAT of 30 U/L or more), and low platelets (platelet count of less than 100 x 10^9 / L).

Threatened preterm labor. Documented uterine contractions before 37 weeks of pregnancy, with or without evidence of cervical changes.

Antepartum hemorrhage. Objectively assessed blood loss from the genital tract outside of parturition.

Preterm rupture of membranes. Rupture of the membranes with amniotic fluid loss before the 37th week of pregnancy, diagnosed by sterile speculum vaginal examination with visible amniotic fluid and a positive fern test.

Gestational diabetes. Postprandial venous blood glucose values of 7 mmol/L or more after 20 weeks of gestation in a woman without known preexisting diabetes mellitus.

Term birth. The fetus or newborn is referred to as "term" when delivery occurred in the interval from the 38th to the 42th week after the onset of the last normal menstrual period.

Preterm birth. The delivery occurred before 37 completed weeks of gestation.

Postterm birth. The delivery occurred after 42 completed weeks of gestation.

The newborn

Apgar score. The condition of the newborn was evaluated by the use of a scale from 0 to 2 for each of the infant's vital functions (heart action, respiration, color, tonus and reflexes), at one and five minutes after birth.

Appropriate-for-gestational age (AGA). The Kloosterman growth curve[110] was used to assess the weight of the newborn in relation to gestational age, sex of the infant and parity of the mother. Birthweight between the 10th and the 90th percentile of the growth curve indicates an AGA infant.

Small-for-gestational age (SGA). A birthweight below the 10th percentile of the growth

curve.

Very small-for-gestational age (VSGA). A birthweight below the 2.3rd percentile of the growth curve.

Birthweight ratio. The ratio is calculated by dividing the actual weight at birth by the weight the infant should have had according to the 50th percentile on the growth curve at the same gestational age. The ideal birthweight ratio is 1.

Length ratio and head circumference ratio. The ratios are calculated according to the same principle as birthweight ratio using the 50th percentile of the length and head circumference curves of Usher and Mc Lean.

Withdrawal syndrome in the neonate. The syndrome includes signs of the central nervous system, digestive and respiratory tracts (jitteriness, tremors, high pitched cry, hypertonicity, snuffles, sleep disturbance, yawning, vomiting, diarrhea, abnormal feeding pattern, tachypnoea, sneezing, fever/excess sweating, convulsions etc), caused by the postpartum withdrawal of opiates in the newborn.

Stillbirth. At or immediately after birth there are no signs of life in the infant born after 16 weeks of gestation. The term is synonymous with fetal death.

Neonatal death. A death that occurred in the first 28 days of life, irrespective of birthweight or gestational age.

Perinatal mortality. Stillbirths plus neonatal deaths.

2.3 Assessment of variables

The study protocol included assessment of the following predefined variables in the study group and, where applicable, in controls:

a. Age
b. Parity
c. Number of abortions
d. Drug abuse
    1. type of substance abuse - drug associations
    2. daily amount of drug use until the diagnosis of pregnancy (if possible daily drug dose around the conception period) and at enrollment in the antenatal care program
    3. methadone substitution at first obstetric visit and participation in a

methadone program

4. urinalysis on drug metabolites during the course of pregnancy
5. daily methadone substitution, at discharge after delivery
6. objectively assessed termination of any drug abuse during pregnancy (becoming "clean" during pregnancy)

e. Smoking and daily consumption of alcohol

f. Socioeconomic variables

1. accomodation
2. resources
3. situation of previous children

g. Gestational age at the first obstetric visit

h. Infections, actual and/or in patients history

1. syphilis
2. hepatitis B
3. gonorrhea
4. HIV

i. Complications of pregnancy. Hospital admission.

j. Ultrasound examination as standard screening for congenital anomalies and fetal growth assessment

k. Number of antenatal visits until delivery

l. Delivery

1. gestational age at delivery
2. meconium-stained amniotic fluid
3. vaginal deliveries in head or breech presentation
4. operative deliveries (forceps and vacuum extraction)
5. cesarean section
6. placental weight
7. placental anomalies

m. Newborn

1. fetal death
2. Apgar scores at 1 and 5 minutes after birth
3. weight, length and head circumference measurement immediately after birth

4. birthweight, expressed as percentile of the standard growth curve
5. weight, length and head-circumference ratios
6. signs of neonatal withdrawal syndrome
7. stillbirth, neonatal and perinatal mortality

n. Final psychosocial report and recommendation of Central Address
1. positive
2. negative
3. undecided at the time of discharge of the mother

2.4 Standard protocol of antenatal and perinatal care

For every pregnant woman the antenatal care in the University Hospital Rotterdam follows a standard protocol that is expanded to include more specialistic obstetric care when necessary. Such an expanded protocol was developed for substance dependent pregnant women and will be presented in 2.5.

Women are encouraged to enroll for antenatal care 8-12 weeks after their last normal menstrual period. At the first obstetric visit a comprehensive interview and examination is performed, including laboratory tests and an optional ultrasound examination. Antenatal care is provided by obstetricians and by residents in training for the specialty; midwives are not involved.

Interview

The interview reviews the personal and family history, with special attention to the obstetric history and to diseases which could influence or be influenced by pregnancy. Information is obtained about the health and whereabouts of infants born previously (estimation of obstetric risks). Every pregnant woman is broached with tact about smoking, use of alcohol and drugs.

Physical examination

The woman's general condition is assessed by means of a physical examination, with attention to weight, length, signs of anemia, presence of skin lesions or signs of trauma, blood pressure and possible diseases of the cardiovascular, respiratory, nervous and

locomotor system which could influence or be influenced by pregnancy. Maternal weight and weight gain are recorded on a pregnancy card. When necessary, other medical specialists are consulted. In particular, an obstetric physician, a psychiatrist, and a sexuologist are always available for consultation. A standard gynecologic examination is performed, including a cervical smear.

Laboratory tests

Laboratory tests include determination of blood group and rhesus factor; hemoglobin concentration; hematocrit; platelet count; serum concentrations of aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT), and creatinine. All patients are tested for syphilis by using Venereal Disease Research Laboratory slide test (VDRL), and treponemal hemagglutination test (TPHA), followed by a Fluorescent Treponemal Antibody Test (FTA) when the first two tests are doubtful or positive for syphilis; hepatitis B antigen and antibodies; and HIV, the latter after informed consent at the first antenatal visit. Women diagnosed with early or latent syphilis are treated and followed by a specialist in venereal diseases. Women native to The Netherlands have been vaccinated for Rubella, with rare exceptions, but not allochtones. For that reason, the Rubella titer is only determined in immigrants, and, if negative, a Rubella vaccination is scheduled after delivery.

Ultrasound examination

The gestational age, calculated by dates, is checked in all patients by ultrasound examination and adjusted if necessary. All women undergo ultrasound screening for fetal structural abnormalities at 18-20 weeks gestation. Suspicion or diagnosis of malformations leads to amniocentesis for detection of chromosomal abnormalities and neural tube defects, after informed consent has been obtained, followed by genetic and pediatric counselling. In case of severe fetal abnormalities the woman may opt for termination of pregnancy, depending on gestational age.

Follow-up

The standard schedule for subsequent antenatal visits is every four weeks until 28 weeks of pregnancy, then fortnightly until 36 weeks and weekly thereafter until delivery. The

frequency of the visits is increased when the course of pregnancy is considered abnormal. The repeat antenatal visits include inquiries about general health, fetal movements, vaginal discharge, bleeding or pain. Weight, blood pressure and fundal height are recorded and a urine test is performed to diagnose proteinuria and glucosuria. After 28 weeks the lie, presentation and position of the fetus are assessed, and fetal heart sounds are checked. Ultrasound and laboratory investigations are added when indicated.

Parturition and postpartum care

Delivery takes place in the hospital under the supervision of an obstetric resident or a gynecologist. Seropositive patients deliver according to a special hygienic protocol, that is also used when the HbsAg or HIV status of the parturient is not known. Fetal monitoring is performed when indicated. Intramuscular administration of 75 mg of pethidine, once or twice during the first stage of labor, after assessment of fetal well-being, is generally sufficient for pain relief, but epidural analgesia may be applied. All neonates are examined at birth, and weight, crown-to-heel length, fronto-occipital head circumference, biparietal diameter and physical anomalies are recorded. Neonatal condition is assessed by means of Apgar scoring at one and five minutes after birth. Determination of umbilical arterial acid-base values is performed only if considered indicated. A pediatrician is always available in case of fetal distress during parturition or when any neonatal pathology is to be expected.

Following an uneventful delivery with a healthy mother and newborn, mother and infant leave the hospital within 24 hours and spend the childbed at home under the care of a midwife or the family physician until the 8th day postpartum. If an operative delivery (forceps, vacuum extraction, cesarean section) was performed, mother and infant will remain in the hospital for 2 to 7 days postpartum. The obstetrician and the pediatrician are both responsible for the discharge of mother and child.

Family planning and contraception are discussed before discharge. A consultation in the outpatient clinic is scheduled for 6 weeks after delivery, with extra time allotted for patients who have had a stillbirth, a malformed infant or a complicated pregnancy, delivery or puerperium.

2.5 Protocol of antenatal care for drug dependent pregnant women

Interview

In addition to the standard obstetric, medical and family history, a history of substance abuse was obtained in all pregnant women with self-reported drug use or referred as drug dependent. The history of substance abuse included information that could be obtained about the kind of drug, duration of use, route of administration, pattern of use, regular daily dose, drug-associations, diseases that occurred as a complication of drug use, smoking (regular cigarette abuse), alcohol consumption (daily ingestion of liquor) and social implications of drug use, e.g. prostitution. The obstetrician broached, with patience and tact, socioeconomic subjects related to the patient's drug use that may influence the course and outcome of pregnancy, such as : family composition, history of psychoactive substance use by other family members, in particular by the partner, residence of children born before the present pregnancy, source of income, accommodation, life-stress events in present or past time, presence of supportive persons: family, friends, etc. Information was obtained about the woman's motivation to become pregnant and about her plans as a future mother. Informed consent was asked to establish contacts with the general practitioner, other medical specialists, institutions for the care of drug addicts, social workers etc. All information was exchanged confidentially and provided only to those it concerned. The woman could always withdraw her consent.

In order to establish optimal report, each drug dependent woman was seen by the same obstetrician during her whole pregnancy. During the period 1983-1992, the antenatal care of substance dependent pregnant women was performed by three obstetricians and the author of this thesis, each of them for a period of 2-4 years. They were trained and experienced in taking care of pregnancies complicated by drug abuse and fully informed of the Rotterdam multidisciplinary approachs. Residents in training were not involved in the antenatal care of these patients. All medical decisions involving a drug dependent pregnant woman were taken after consultation with the obstetric care provider for drug dependent women, or, in his absence, the chief of department.

Physical examination

The standard physical examination was performed as in other pregnant women. Careful attention was payed to weight related to length, signs of anemia, scars, skin infections,

signs of trauma, sequelae of diseases related to drug use, e.g cardiac valvular defect as consequence of endocarditis.

Laboratory tests

In drug dependent patients swabs from the rectum, cervical canal, urethra and tonsils were taken at the first visit for culture of N. Gonorrhea. A smear for cervical cytology was always made. The tests for syphilis and hepatitis B, and the N. Gonorrhea cultures were repeated in the third trimester of pregnancy, around 32 weeks gestation. Screening for tuberculosis was not routinely performed.

In patients who were suspected of drug abuse but denied it, urinalysis was done with the patients' knowledge and consent. Suspicion could arise when the patient, without clear reasons, presented late in pregnancy for the first antenatal visit, missed multiple visits, had a history of drug related medical problems, i.e. subacute bacterial endocarditis, skin abscess etc., had children who were not currently living with her or were brought under the care of child-protective institutions. Refusal of urinalysis and persistence of the suspicion to drug abuse during pregnancy resulted in a notification to the pediatrician for postpartum neonatal observation. When a woman denied drug use despite positive toxicologic tests, or refused to be tested, she was closely observed and attemptes were made in following visits to obtain information about drug use. However, for as long as the woman did not admit drug use, she was not included in the study.

Ultrasound examination

Ultrasound examination to confirm the calculated gestational age and to screen for fetal structural abnormalities was performed at 18-20 weeks gestational age in all pregnant women. Suspicion of fetal anomalies was followed by a genetic consultation, amniocentesis and genetic and pediatric counselling. In case of severe fetal malformations, the patient, depending on her gestational age, could opt for termination of the pregnancy. The severity of the malformation, as well as the possibilities for treatment after birth, were the crucial elements in counselling, not the dependence on drugs.

A second ultrasound examination was carried out at 32 weeks of pregnancy to evaluate fetal growth.

Follow-up

The schedule of antenatal visits was the same as that for other pregnant women. The regular antenatal visits included specific inquiries about the current status of drug use (illicit drug use, daily methadone dosis) and about maternal and fetal signs of drug withdrawal. The growth of the fetus was carefully checked. Repeat urinalysis for drug metabolites was performed. All women who reported having terminated their drug use, with or without methadone substitution ("clean" patients), underwent weekly checks (three times a week) on drug metabolites during pregnancy, delivery and puerperium.

Complications of pregnancy; hospitalization

When hospitalization was necessary for obstetric reasons, methadone substitution therapy - if applicable - and the urinalyses were continued in the hospital. The detection of illicit drug use while in the hospital resulted in an increase in the daily methadone dose; persistent abuse of opiates and cocaine, despite warning and extra methadone administration, associated to asocial behavior during hospitalization, could lead to discharge and ambulatory continuation of the obstetric treatment at home.

Parturition and postpartum care

Delivery took place in the hospital under the supervision of a gynecologist, usually, but not always, the one who took care of the patient during the antenatal period. A final urinalysis for drug metabolites was performed. Fetal monitoring was applied in all drug dependent patients. Information was obtained about the last use of drugs, and she was carefully observed for illicit use of drugs during parturition. During delivery pethidine was administered by intramuscular injection, if considered necessary. Drug need and pain were generally sufficiently supressed with pethidine 75 mg i.m., administered once or twice during the first stage of labor; epidural analgesia was applied when considered necessary. Methadone administration during labor was restricted to signs of drug withrawal in mother and/or fetus.

Apgar scores were determined after one and five minutes, but also in these newborns determination of umbilical acid-base values was not routinely done. In case of doubt the Dubowitz score was used for the clinical assessment of gestational age[57].

The pediatrician was always present at delivery and was fully informed about the course

of pregnancy, history of drug use and about the medication used during labor. All newborns of drug-dependent women were examined by the pediatrician and observed for at least one week, in order to detect signs of the neonatal withdrawal syndrome. When a neonatal withdrawal syndrome was suspected, urinalysis was performed to detect drug metabolites. All placentas from drug dependent mothers were examined macroscopically and, between 1983-1988, histologically. The routine histologic examination was abandoned in 1989.

Drug dependent mothers were recommended to stay in the hospital for 5-7 days after delivery. Mothers and infants were carefully observed by the medical and nursing staff, and mothers were trained to take care of their babies. Mothers who had been unable to stop substance abuse during pregnancy were not encouraged to breast feed, but others were. Bonding between mother and infant received special attention.

Contraception and family planning were discussed before discharge. Since many drug dependent women tend to neglect contraception, special attention was given to provide the women with appropriate information and to motivate them to take contraceptive measures. However, contraceptive measures were advised but never imposed. Providing the optimal advice to an individual woman, it was taken into account that oral contraception is often unsuccessful in drug dependent women because of poor compliance; that the intrauterine device is not the safest choice because of the high risk of sexually transmitted diseases existing in this population; that barrier methods are less effective and may not be used properly and regularly. An intramuscular injection of a depot preparation of hydroxy-progesterone was the most frequently recommended contraceptive, although it does not offer protection against sexually transmitted diseases. Sterilization could be performed six weeks after delivery, only on patients' request and after ample consideration, but this was generally not the first choice of contraception. A gynecologic consultation was scheduled six weeks after delivery, as in the standard protocol.

When the newborn required further medical care, e.g. because of a neonatal withdrawal syndrome, prematurity, small-for-gestational age etc. or when no supportive social measures could be arranged for mother and child, the baby remained in the Department of Neonatology of the University Hospital Rotterdam (Sophia Children's Hospital). During the infant's stay in the hospital, the parents received a daily task program for taking care of the baby under the supervision of the pediatric nursing staff. They were taught to deal

not only with the physical and emotional problems of the baby born after a pregnancy complicated by drug abuse, but also with their own distrust in their capabilities as parents. All infants born to drug abusing mothers received a standard pediatric follow-up for at least one year by a pediatrician with experience in this field, irrespective of whether or not the infant lived with its parents. During a period of ten years, two pediatricians offered specialized pediatric care for children of drug dependent parents.

Counselling, detoxification, and psychosocial support

All drug dependent patients were informed at their first antenatal visit about the importance of good antenatal care; about the urine tests that would be done on a regular basis with or without participation in a methadone program; about their future delivery and puerperium; and about the necessary observation period for their newborn. Medical, social and sometimes legal implications of parenthood associated with drug dependency were discussed and all drug dependent patients were informed about the further approach as organized in Rotterdam. Informed consent was asked to establish contacts with the general practitioner, other medical specialists, institutions for the care of drug addicts, and social workers etc.

All drug dependent pregnant women were stimulated to switch from heroin to oral methadone and to enroll in a methadone program. Treatment for drug dependence was carried out under the supervision of a physician specialized in substance dependence. However, the final decision was left to the woman. If the patient was motivated to change her drug habit, detoxification could take place on an ambulatory basis or in an inpatient program. Patients who chose for a therapeutic community remained there for treatment, not only during pregnancy but also after delivery, with their child.

In the methadone maintenance program, the heroin dependent woman switched to oral methadone, and received a daily methadone dose sufficient to prevent withdrawal symptoms. Stabilization of the daily dosis methadone was followed, when possible, by carefully scheduled lower dosages as recommended by Ostrea et al[155] and Connaughton et al[41]. Reduction of the daily methadone dose was started on the patient's request, when there were no medical contraindications for detoxification, the patient's psychosocial situation was stable and the obstetric care provider and her mentor from the drug program did not have any objections. The objective of methadone maintenance was to reach the lowest

effective, rather than the lowest possible dose[41,65,66,67,69,128,191]. When possible, the woman's partner was engaged in the agreements around her drug use and antenatal care. The detoxification schedule started when the toxicologic tests demonstrated that she had not used illicit drugs for at least one week after stabilization on methadone. The dose of methadone was then reduced weekly with 1-4 mg under daily control of withdrawal symptoms, and three times weekly urinalysis on drug metabolites[41]. Special detoxification schedules were used for women on drugs other than or in addition to opiates, e.g benzodiazepines; the dose of these drugs was also reduced weekly. According to the protocol, detection of illicit opiate and/or cocaine abuse resulted in an increase of the daily methadone dose or in a cessation of the detoxification schedule. Obstetric findings that suggested a decline in maternal or fetal well-being (jittery fetus, preterm contractions etc.) were also considered reasons to stop the detoxification program. Although informed about the patient's daily methadone dose, the obstetrician did not provide methadone, except when the patient was hospitalized. The obstetrician emphasized the importance of social security for both mother and child. An appointment was arranged with the social workers of the Central Address (Department of the Bouman Drug and Alcohol Institution), a special unit set up in Rotterdam for drug dependent parents and their children.

The Central Address attempts to provide a safe environment and shelter for the substance dependent mother and her children, irrespective of the mother's race, nationality, legal position or her willingness to have her drug dependence treated. The Central Address carries out a comprehensive socioeconomic assessment during pregnancy, with emphasis on the following:

1. Assessment of patients' current living conditions, education and resources
2. Substance abuse history and involvement of community agencies
3. Identification of domestic violence and dangerous circumstances
4. Motivation and capacity to serve as parents
5. Assessment of the availability of supportive friends and family

The Central Address cooperates with and coordinates the activities of institutions for social care and child welfare.

A summary of the tasks of Central Address is presented in Fig 2.1.

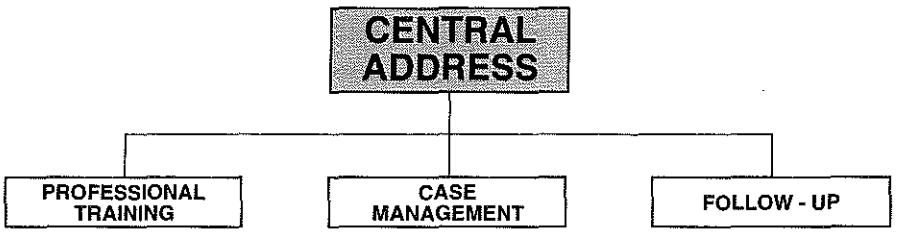


Fig. 2.1 Objectives of the Central Address in the multidisciplinary approach to drug dependent pregnant women.

The organizations associated with the Central Address in the Rotterdam multidisciplinary approach are presented in Fig. 2.2.

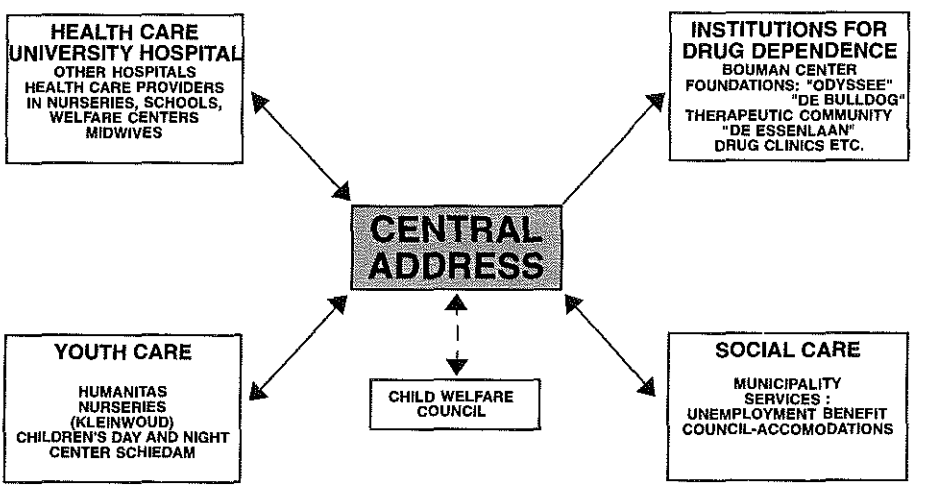


Fig. 2.2 Organizations associated with Central Address in the Rotterdam multidisciplinary approach to drug dependent pregnant women.

Mentors, psychologists, specialized social workers for children of drug-dependent parents, and physicians with experience in pychoactive substance disorders, employed by the Central Address and one of the institutions specialized in drug dependency, were available for the drug dependent pregnant woman enrolled in our antenatal care program. If a drug

dependent woman refused any contact with existing drug programs and social institutions, the Central Address itself made arrangements to support and improve the social situation of the mother in as far as she accepted such assistance. A social supportive plan for the mother and her future infant was developed by the Central Address and the social and child protective organizations during pregnancy, before delivery. An overview of the integrated multidisciplinary network for the care of drug dependent pregnant women and their infants established in Rotterdam is presented in Fig. 2.3.

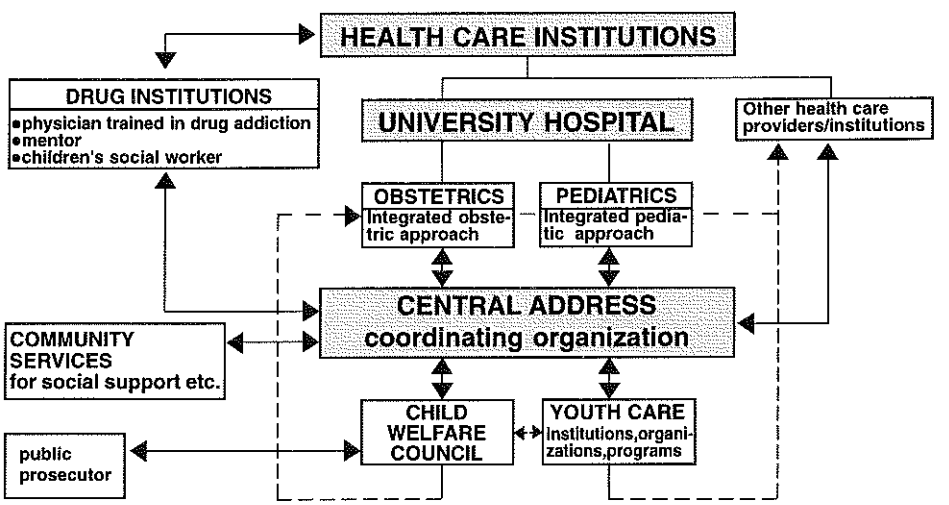


Fig. 2.3 The Rotterdam network for the multidisciplinary approach to drug dependent pregnant women.

The final report and recommendation

The future mother was informed at the first meeting with the obstetric care provider and the social workers of the Central Address, that the Central Address would prepare a report about the socioeconomic and psychosocial conditions that the parents would be expected to be able to offer to their offspring, with a recommendation as to whether or not the baby should be entrusted to its parents. The elements on which the final report would be based (e.g. good parenthood in the past, presence or absence of stabilization of drug use, of

financial support, of acceptable accomodation etc.) were presented to the pregnant woman and, if possible, her partner, at the intake, in order to give her full opportunity to make positive changes. The final report of the Central Addres has no legal prerogatives. Positive and negative changes in pregnancy, related to termination or stabilization of drug use, attempts to social integration, concern for the actual pregnancy as indicated by frequent antenatal visits, illicit drug use, cooperation with social institutions, briefing for child care etc. were included in the final report. In case of a positive final report, the infant was entrusted to the care of its parents. The Central Address remained responsible for the follow-up of the child and its family and for the coordination of additional social supportive plans when necessary. A negative final report resulted in a request to the Child Welfare Council to further investigate the situation of mother and child. A negative report was based on failure of the social and child-protective organizations to reach reliable agreements with the parents for a social supportive plan and it meant that the socioeconomic and psychosocial conditions to be expected after delivery were considered inappropriate to create a safe environment for the infant.

In some cases the Central Address was unable to deliver a definitive advice before delivery, for instance when the woman presented very late in pregnancy. In case of a negative final report or when no report was available, the Child Welfare Council and the Court were responsible for finding a suitable solution. This could be an imposed social supportive plan, or a foster plan, to offer a safe environment for the infant. In such cases the infant remained in the Department of Neonatology of the University Hospital Rotterdam for observation and this period of time was used to observe the development of parent-child bonding and to get an impression about the developments to be expected if the infant would be entrusted to its parents. When there was clear evidence that psychosocial support for the infant at home would be insufficient, the infant remained in the Department of Pediatrics of the University Hospital Rotterdam until the Child Welfare Council had found a suitable environment, usually in a foster home.

A schematic presentation of the extended and standard protocol for drug and non-drug dependent pregnant women is shown in Fig. 2.4.

2.6 Statistical presentation and analysis

The observations are presented and analyzed using nonparametric methods since the

variables studied could not be accepted to follow normal distributions in the majority of cases. Descriptive statistics are numbers, means, medians (ranges) and (relative) frequencies.

Odds and ratios of odds are presented where appropriate, with their 95% confidence intervals. Differences between continuous variables were assessed with the Wilcoxon signed rank test in paired observations, and with the Wilcoxon rank-sum test in two samples. Relationships between continuous variables were analyzed with Spearman's rank correlation test. The x^2 test or Fisher's exact test was used to analyze discrete data. Because of the multiple comparisons the probability level (P-value) required to reject the null hypothesis (significance) was set at $p \leq 0.01$.

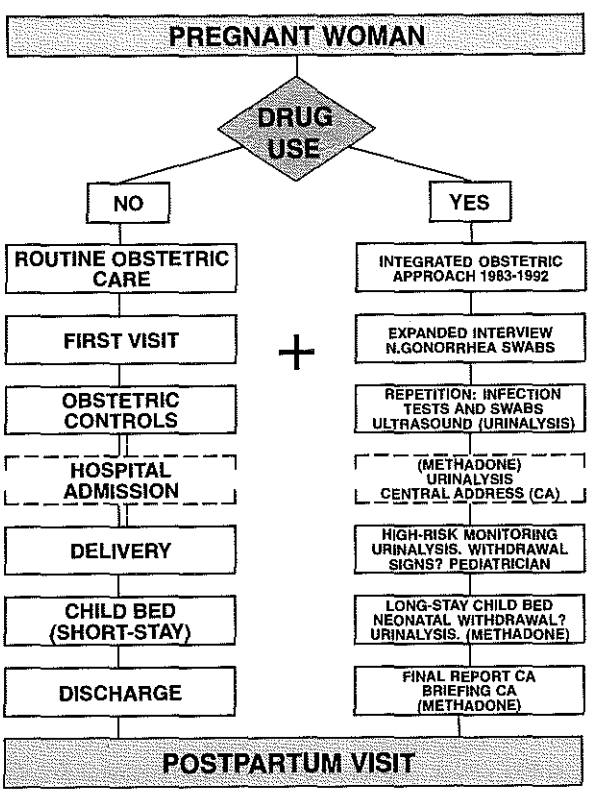


Fig. 2.4 Schematic presentation of the standard and expanded obstetric protocol for drug-free and drug dependent pregnant women.

Statistical analyses were performed using the SPSS program (Statistical Package for the Social Sciences)-SPSS/PC + V4.0.

2.7 Discussion

In the seventies, programs for treatment of drug dependence in the United States[19,21,41,84,89,103,193,206] emphasized the importance of adequate drug substitution and social support during pregnancy. In that time antenatal care for drug dependent pregnant women was generally reported to be poor; only one in four addicts was booked before labor [160] and of those more than 50% were already in the third trimester of pregnancy[192]. No consistent measures were taken to improve the enrollment of these women in an antenatal care program. It seemes likely that the poor obstetric and neonatal outcomes of pregnancies in drug dependent women reported from the United States in that period of time were not only due to drug abuse, but also to insufficient antenatal care and poor socioeconomic status[161,212,213,214]. In the late seventies various authors[41,65,84,89,192,193] pointed out that early enrollment and adequate antenatal care are important means to improve the obstetric outcome in drug dependent women, but these issues received little attention until 1985 when Finnegan[69] emphasized the importance of integrated medical and psychosocial care in the obstetric programs for drug dependent women.

Longitudinal, prospective studies are ideal in evaluating the full spectrum of physical, mental, behavioral and psychological changes in those exposed to toxins or teratogens, but they confront the community with high costs and extensive logistics. An additional deterrent refers specifically to drug abuse. Anonimity is a basic requirement of research in this area since drug abuse may have important legal and social consequences. Even if the study warrants participants their anonimity, it still remains difficult to convince drug abusing people not only to supply health and socioeconomic information, but to agree also with the impartial checking of the provided information and the participation in a long term follow-up study that often requires more discipline than they can afford. The development of an unbiassed study design concerning drug addiction is therefore a real challenge for researchers.

The observational study presented in this thesis was designed to assess the results of the integrated multidisciplinary approach to obstetric care of drug dependent women in Rotterdam, from 1983 to 1992. Although this is a retrospective study, the standardized protocols for collection of pertinent socioeconomic data in drug using women, and for documentation of antenatal and perinatal care and of course and outcome of pregnancy in the study group as well as non-drug dependent women, were meant to be evaluated after

a certain period of time. For that reason most, although not all, information may be expected to be complete. Outcomes in drug dependent patients were compared with those in nondependent pregnant women matched for a small number of variables related to obstetric outcome but considered irrelevant as an endpoint in the study: parity, age, and singleton pregnancy. Women could not be matched with regard to cigarette smoking, a highly relevant variable. Almost all drug dependent women smoked, and a sufficient number of smoking controls could not be found. Also socioeconomic criteria were not included in the matching. Results of studies of Miller et al[137,139] suggest that factors such as absence of antenatal care, smoking, use of drugs and large amounts of alcohol may be more important determinants of pregnancy outcome than socioeconomic circumstances. In general, the majority of the drug dependent women may be classified in a low socioeconomic level, but the same is true for the general obstetric population in the outpatient clinic of the University Hospital Rotterdam from which the control group was drawn. Because of incomplete documentation, race was not recorded.

The often chaotic lifestyle of drug dependent pregnant women makes that appointments and responsibilities are frequently put aside for the search for drugs. For this reason, a network of midwives, physicians and social workers of drug institutions was organized in 1983 in Rotterdam in an attempt to increase the referral rate and to persuade drug abusing pregnant women to enroll in antenatal care early in pregnancy. The aims were the start of antenatal care before 20 weeks of pregnancy, and a quantity and quality of antenatal care similar to that received by drug-free pregnant women. The time schedule arranged for the visits to antenatal outpatient clinic of the University Hospital Rotterdam was the same for drug dependent as for non-dependent pregnant women. A schedule with a higher frequency of visits for drug abusing women was considered unrealistic because of the difficulty these patients usually have keeping their appointments. It was included in the protocol already in 1983 that a single obstetrician and a small team of well-trained care providers should establish a personal relationship with the drug dependent pregnant woman and provide antenatal care. The view that such an approach could contribute to the continuity of antenatal care of drug dependent women received more and more support after 1985 [69] and has become a general recommendation since 1990[5,66,107,186].

Although the fact that a woman is drug dependent will often be known to the obstetrician at the time of intake for antenatal care, the number of women that try to hide their

dependence cannot be neglected as shown by prevalence studies[26,71,80,130,131]. For that reason, it is of great importance that the obstetrician recognizes signs and symptoms of drug abuse in the history and at physical examination. A history of drug-associated disease such as hepatitis, bacterial endocarditis, multiple abscesses etc, and the presence of pupillary constriction, scars, thrombotic veins, subcutaneous nodules or abscesses, localized edema over superficial veins and lymphadenopathy at the physical examination are suggestive of intravenous drug abuse[66]. Suspicion should arise when the patient consistently fails to have laboratory tests performed because of lack of accessible veins. Analysis of urine specimens on drug metabolites makes the diagnose of drug use definitive[75,128]. Informed consent should be elicited from the woman before a urine toxicologic screening test is initiated. This consent does not have to be given on a test-by-test basis if the woman is informed of the program policy at the initial visit and agrees to participate [81] but the woman may withdraw her consent at any time. In the outpatient clinic of the University Hospital Rotterdam urinalysis was used consistently from 1983. The clinician had the responsability to explain the rationale for drug screening, discuss who would be informed of the result, and clarify any misconceptions that the woman might have. Although the literature before 1983 mentions the use of urinalysis on drug metabolites if a pregnant woman was known or suspected to be drug addicted[89], it is only after 1983 that the importance of urine screens in addition to a thoroughly taken history is emphasized by prevalence studies[26,71,203]. The survey of The National Association for Perinatal Addiction Research and Education - USA in 1987 found an elevated incidence of positive diagnoses of substance abuse when the patients were screened according to specific protocols.

In the Rotterdam protocol, all drug dependent pregnant women were stimulated to enroll in an ambulatory or inpatient methadone program. Substitution of heroin with oral methadone prevents the peaks and valleys in the maternal heroin level; it may reduce the exposure to HIV-infection, and eliminate other dangers of intravenous administration of heroin and of illicit behavior and, through that, may limit contact with the drug-seeking environment and may make drug dependent pregnant women amenable to antenatal care and psychosocial support programs[41,65,66]. Although the policy aimed at methadone maintenance with gradual detoxification[6] when possible, there was no requirement of mandatory detoxification.

The protocol for antenatal care in drug dependent patients concentrated on screening for

complications that are characteristic of these pregnancies. The specific investigations included microbiological tests and ultrasound examinations. Tests on syphilis, hepatitis B, N.Gonorrhea and, since 1985, HIV were carried out repeatedly since a high incidence of sexually transmitted diseases is reported in drug dependent pregnant women[36,41,89,192] Already in 1979 de Lange[116] mentioned the necessity of N.Gonorrhea cultures in heroin addicted pregnant women, but none of the studies published before 1983 reports the use of standardized bacteriological examinations for N.Gonorrhea or of repeat serological determinations for syphilis and hepatitis B.

The occurrence of fetal growth retardation in pregnancies associated with drug abuse was already frequently reported before 1983[41,43,99,104,120,147,160,161,192]. For this reason, an additional ultrasound examination was scheduled as a routine for drug using pregnant women at 32 weeks of pregnancy to assess fetal growth. Although a direct relationship between congenital malformations and drug abuse could not be established in studies published before 1983[156,161,190,213], an ultrasound examination was included in our obstetric protocol to be performed at approximately 20 weeks gestation, in order to ascertain the presence or absence of fetal anomalies. Later publications support the ultrasound screening for fetal abnormalities in this group of patients[13]. In 1983 the long-term effects of intrauterine drug exposure on the infant were hardly known. Since some studies[70,209] raised the issue of possible cerebral dysfunction, longterm pediatric follow-up was instituted in the program to assess the impact of drug abuse in pregnancy on growth and development of the children.

Quite often pregnant substance abusing women cherish an idealistic expectation about pregnancy and motherhood, which they regard as a hopeful event in their chaotic life, dominated by the search for drugs[15]. With an unfinished education, unemployed, estranged from family and friends, often with traumatic life experiences and without social control and support, such hopes are usually unrealistic. Drug dependent women easily fall into prostitution and deliquency, and the traditional role of primary caretaker of children is difficult to fulfil when drugs impair the judgment and capacities of the mother. In the multidisciplinary approach to obstetric care for drug dependent pregnant women in Rotterdam, the Central Address functions as a bridge between various institutions for health and social care for drug dependent parents. It aims to create possibilities for drug dependent mothers to rear their offspring in a safe environment. The design and functioning

of the Central Address are unique, because this organization coordinates psychosocial support for drug dependent parents for the whole city of Rotterdam. As part of the Bouman Foundation, the Central Address offers drug dependent parents access to all available facilities, but it is not acting in the interest of any of the drug, social or child care institutions. No other example of an approach in which the health care of drug dependent pregnant women of a whole city is concentrated in a single hospital and the psychosocial supportive program of all drug abusing mothers in the city is organized and supervised through a central, impartial, institution could be found in the literature.

Chapter 3

CHARACTERISTICS OF THE DRUG DEPENDENT POPULATION

In this chapter characteristics are presented of the drug dependent pregnant women and their controls, matched for age and parity (Chapter 2). Patterns of drug abuse and of selected socioeconomic variables are reported.

3.1 General characteristics

The mean age of study patients and controls was 26,5 years. Figure 3.1 shows the numbers of drug dependent pregnant women booked for antenatal care in the University Hospital Rotterdam over the 10 years period of the study.

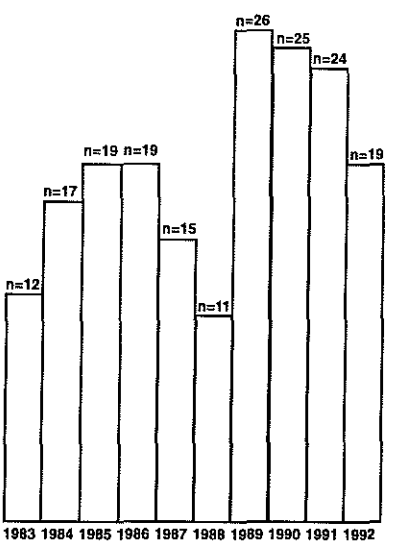


Fig.3.1 Annual booking of drug dependent pregnant women for antenatal care in the period 1983-1992.

The distribution of gravidity and parity of the study population and controls is presented in Figures 3.2 and 3.3. Parity was a matching criterion, whereas gravidity was not.

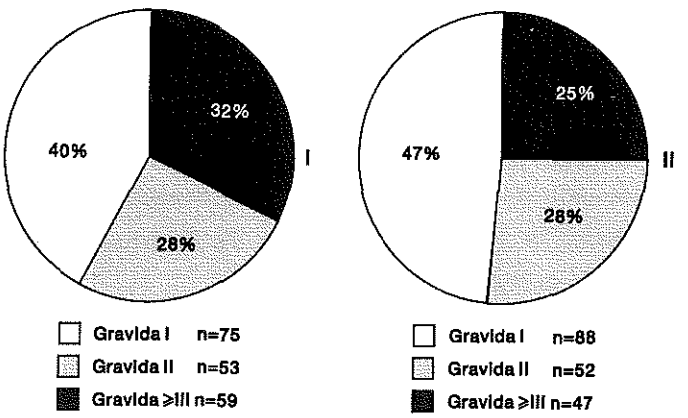


Fig.3.2 Gravidity in the drug dependent pregnant women (1) and controls (2).

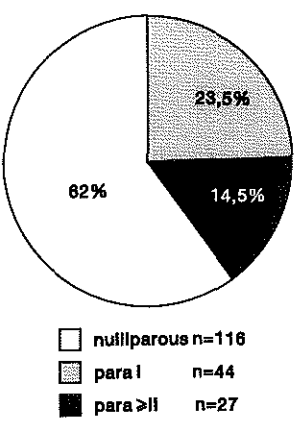


Fig.3.3 Parity in the drug dependent pregnant women and controls.

3.2 Patterns of drug use

At booking, the drug dependent pregnant women enrolled in the study were using mainly opiates (heroin with or without methadone) and cocaine, usually in combination with opiates. The usual route of intake of heroin appeared to be intranasal or smoking, but in 28 cases evidence was found of recent intravenous administration. The majority of the drug

dependent women admitted having used heroin intravenously at some time in the past. Pure heroin use was encountered in particular in the first 6 years (1983-1988) of the study (13 cases). After 1985 the use of opiates became frequently associated with that of cocaine. Considering the cocaine use over the 10 years period of this study, as presented in Table 3.1, it is to be noted that 75% of the drug dependent women enrolled for antenatal care in the last four years admitted the use of and tested positive for cocaine.

Table 3.1. Cocaine use in the periods 1983-1988 and 1989-1992 (numbers and percentage).

	Period 1983-1988 n=93	Period 1989-1992 n=94
Documented cocaine use ■	26 (28%)	70 (75%)
No documented cocaine use	23 (25%)	17 (18%)
Incomplete documentation	44 (47%)	7 (7%)

■ Admitted by the woman and/or positive at urinalysis.

The decrease in the number of cases with incomplete documentation of cocaine use between the first (47%) and the second (7%) period may reflect the increasing awareness of the problem on the part of the obstetric care providers. At the time of booking, polydrug use (combinations of opiates and/or cocaine with at least one of the following drugs: benzodiazepine, barbiturate, analgetics) was documented in 25% of the drug dependent pregnant women (47 cases). Marijuana and pure amphetamine use were not included in the study. The information obtained from the pregnant woman or her partner by interview regarding the usual, maximum and minimum intake of opiates and/or cocaine was considered unreliable and for this reason could not be used for further analysis.

Seventy-seven percent of the opiate dependent pregnant women switched to the use of methadone, while 23% remained on heroin and cocaine. In contrast to the illicit drug use, the daily dose of methadone prescribed as part of the methadone program is known. According to the literature[66], the daily dose of methadone was considered low (< 40 mg), medium (40-60 mg) or high (>60 mg).

Based on self-reports, urine tests, information received from the methadone programs and other treatment facilities and the drug use documented at postpartum discharge, the group of 187 drug-dependent pregnant women was divided into 3 subgroups according to their drug status at postpartum discharge:

1. Group 1 : the "clean" group, includes drug dependent pregnant women who, with or without the support of a methadone program, reduced and then completely stopped and maintained abstinence from all methadone and illicit drug use during pregnancy (n=51). Patients with a positive history of drug dependence and self-reported heroin and/or cocaine use in the present pregnancy who did not switch to methadone (n=18) but succeeded in terminating their drug use in pregnancy as documented by negative urine tests were included in this group. The drug dependent women included in this group had an estimated history of drug use before pregnancy from 2 to 17 years.
2. Group 2 : the "methadone" group, includes drug dependent (heroin, cocaine) patients who switched to oral methadone in a methadone program. They stopped their illicit drug use and then reduced their methadone use with a minimum of 25% of the initial dose, but were unable to completely stop and abstain (n=47). The estimated duration of drug dependency varied from 1 to 15 years. Illicit drug use as documented by urine tests (3 times a week) was absent or incidental (not more than twice during pregnancy).
3. Group 3 : the "polydrug" group, consisting of drug addicted pregnant women who did not succeed in reducing the amount of drugs used during pregnancy (n=89). In this group there was even a lack of stabilization of drug use as shown by evidence of illicit drug use in addition to the methadone obtained in a methadone program. Patients who continued their heroin/cocaine use during pregnancy without switching to oral methadone (n=25) were included in this third group. The estimated duration of drug dependency varied between 1 and 16 years. An important characteristic of the group is the frequent illicit drug use, despite attempts to stabilization on methadone.

The distribution of drug dependent women among the three categories changed during the study period. Figure 3.4 shows the distribution of the three groups in the periods 1983-1988 and 1989-1992. A significant twofold increase (p=0.01) was observed in the number of patients who became clean in the second compared with the first period, whereas no difference was observed between the two periods with respect to the total number of patients who attended the clinic or the severity of drug dependence at the time of enrollment for antenatal care.

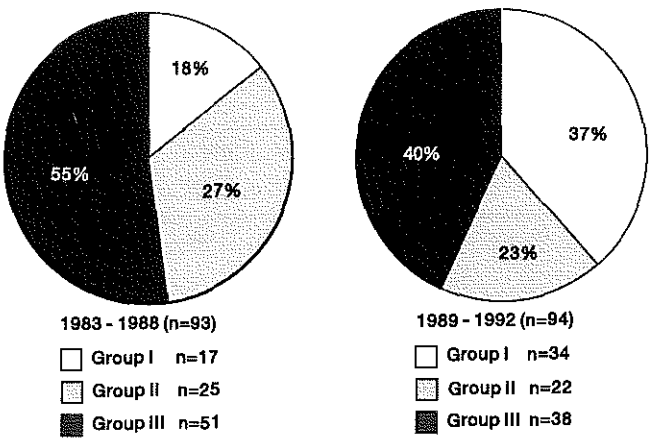
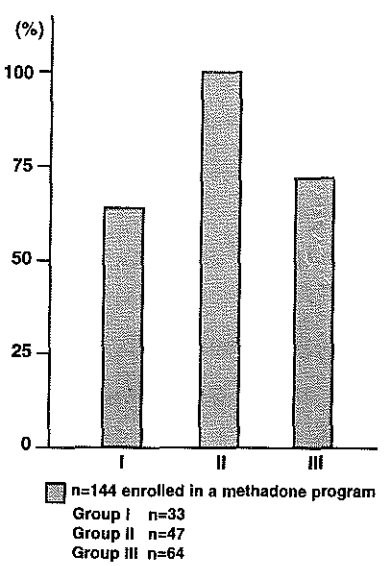


Fig. 3.4 Distribution of drug use in pregnancy in the periods 1983-1988 (left) and 1989-1992 (right).



The relative frequency of enrollment in a methadone program in the three groups of patients is presented in Figure 3.5. The daily dose of methadone at the first obstetric visit and at postpartum discharge is presented in Table 3.2. At booking in the antenatal care program 78% of the 144 patients were on low-dose methadone; the use of medium and high dose methadone was rare in all three categories of drug dependent women.

***Fig. 3.5** Proportions of drug dependent pregnant women enrolled in a methadone program during pregnancy.*

Table 3.2 Distribution of methadone dose in methadone substituted pregnant women at the first antenatal visit and at postpartum discharge.

Daily dose of methadone	Group 1 n=51		Group 2 n=47		Group 3 n=89	
	First visit	Post-partum	First visit	Post-partum	First visit	Post-partum
Low-dose methadone (1-40 mg)	29	0	35	46	48	53
Medium dose methadone (41-60 mg)	3	0	9	1	12	11
High-dose methadone (> 60 mg)	1	0	3	0	4	2

At discharge after delivery, the daily methadone dose was zero for the patients in the first group. The daily dose was at least 25% lower than the initial dose in the "methadone" group, and usually unchanged or higher, and associated with frequent illicit drug use, in the third group. At the end of pregnancy 57% of the women in the polydrug group were still on low-dose methadone. According to the documentation of the Central Address as per May 1994, 49% (n=25) of the drug dependent pregnant women who completely stopped drug use in pregnancy were still clean, 1-10 years after delivery. A relapse in drug use appeared in 31% (n=16) of the patients belonging to the first group, one to eighteen months after childbirth. In the remaining patients (n=10) the drug status could not be documented. The general characteristics of age, gravidity and parity in the three subgroups and their controls are presented numerically and proportionally in Table 3.3 and Figure 3.6.

There were more nulliparous women in the clean group than in the other two groups, but the difference is not significant at the one percent level. Of all drug dependent women, 40% reported having had one or more abortions, elective or spontanous. The percentage abortions was higher in the first (45%) compared with the third group (35%).

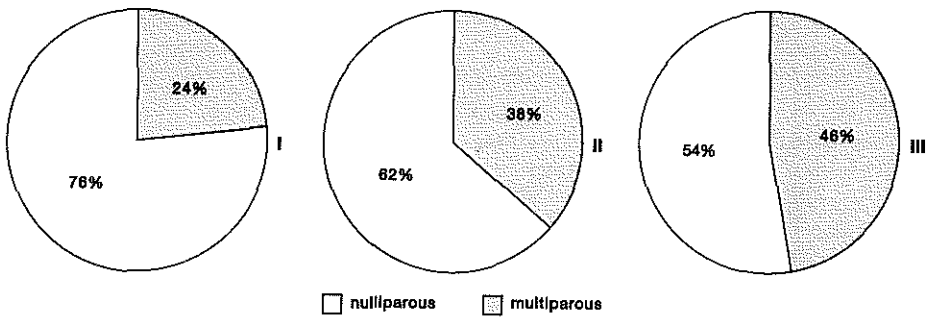


Fig.3.6 Parity in the three groups of drug dependent pregnant women and their controls.

Figures 3.7 presents information about smoking and alcohol habits in the three groups compared with their controls. More than 75% of the drug dependent pregnant women smoked, irrespective the subgroup they belonged to, a significant difference with the 23% smokers in the control group ($p < 0.0001$).

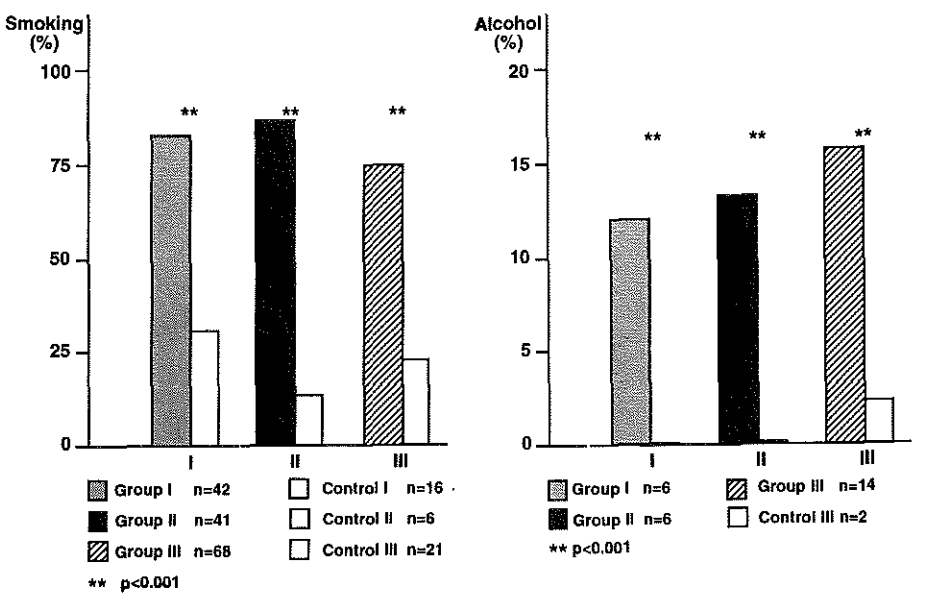
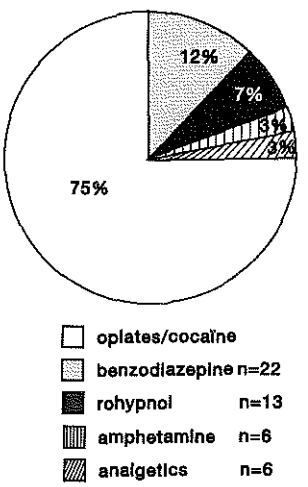


Fig.3.7 Distribution of pregnant women who smoked (left) and consumed daily alcohol (right) during pregnancy in the three study groups and their controls.

Table 3.3 Characteristics of age, gravidity, parity and abortions in the study and control groups.

Characteristics		Study population n=187			Control population n=187		
		Group 1 n=51	Group 2 n=47	Group 3 n=89	Control 1 n=51	Control 2 n=47	Control 3 n=89
Age	Median	26	27	26	26	27	26
	Min - Max	(18-34)	(17-40)	(17-39)	(19-34)	(18-39)	(18-39)
Gravidity	I	23 (45%)	19 (40%)	33 (37%)	27 (53%)	22 (47%)	39 (44%)
	II	18 (35%)	11 (23%)	24 (27%)	16 (31%)	12 (25.5%)	24 (27%)
	≥III	10 (20%)	17 (37%)	32 (36%)	8 (16%)	13 (27.5%)	26 (29%)
Parity	0	39 (76.5%)	29 (62%)	48 (54%)	39 (76.5%)	29 (62%)	48 (54%)
	I	11 (22%)	11 (23%)	22 (25%)	11 (22%)	11 (23%)	22 (25%)
	≥II	1 (1.5%)	7 (15%)	19 (21%)	1 (1.5%)	7 (15%)	19 (21%)
Abortions	0	28 (55%)	25 (53%)	58 (65%)	31 (61%)	33 (70%)	71 (80%)
	I	15 (29%)	16 (34%)	20 (22.5%)	19 (37%)	11 (23%)	13 (15%)
	≥II	8 (16%)	6 (13%)	11 (12.5%)	1 (2%)	3 (7%)	5 (5%)

Daily alcohol consumption was also significantly more frequently reported in the study groups than in controls ($p < 0.0001$).



Some patients used, in addition to opiates and cocaine, other drugs (amphetamines, benzodiazepines, barbiturates, sedatives, analgetics). The consumption of other drugs in addition to opiates and cocaine is presented in Figure 3.8.

Fig.3.8 Proportions of drugs abused during pregnancy in the study population.

3.3 Socioeconomic characteristics

Some of the socioeconomic characteristics of the drug dependent pregnant women in the study group are summarized in Table 3.4. Information about socioeconomic issues was difficult to obtain and may not always be complete. Data on resources and accomodation of polydrug dependent pregnant women is in particular likely to suffer from shortcomings. For that reason no statistical analysis was performed on this data. Drug dependent pregnant women who reduced and terminated all drug use during pregnancy had good or reasonable accomodation in the majority of cases, with the availability of water, gas, electricity, warming system, shower etc., as documented by a visit by a social worker. In the group of polydrug abusers, complete documentation regarding accomodation could not be obtained in 40% of cases. In the group for which reliable data is available, only 37% had reasonable accomodation and 7% admitted to be homeless. A number of women in this group were known to stay illegally in The Netherlands.

The main source of income for all three groups of drug dependent pregnant women was

the unemployment benefit (79%). Only 3% of the drug using women were employed, and 6% were living with an employed partner. In the polydrug dependent group 23% of the women were not recorded as having a legal source of income. Thirty-six percent of all drug dependent patients admitted prostitution in the present pregnancy (15%) or in the past (21%). With regard to prostitution, the highest percentages are found in the group of polydrug users: 20% of the women belonging to this group admitted having prostitution during pregnancy and another 12% addmited to have prostituted themselves in the past. The incidence of prostitution in the present pregnancy in polydrug users was more than twice that in the women who became clean.

With respect to the situation of children, nulliparous women dominate all three categories in the study group.

Social workers from community services provided psychosocial support to the majority of the drug dependent patients included in the first two groups. Thirty percent of the polydrug users group avoided contact with community services, and had no social support during pregnancy. The highest percentage of women who received socioeconomic support (89%) was recorded in the group of methadone users.

3.4 **Discussion**

Clinical studies about drug abuse in pregnancy are inclined to accept a cause-and-effect relationship between the drug that was being abused and the course of pregnancy and perinatal outcome[216]. Yet, there are many potential confounding variables that can mask or distort such a relationship. Therefore, a critical consideration of the shortages and potential pitfalls of this study is necessary for a correct interpretation of the obstetric results that will be presented in the following chapters.

The first element to analyze is the description of the study population and the definition of the control group. As Chasnoff emphasized in 1991[29] it is extremely important to quantify the insult. In this study the reliability of information about the dose, pattern and type of drug(s) used is questionable. In their self-reports addicts are often unreliable and manipulative, and the urinalysis that was done as a routine supplies only qualitative information. Therefore, the data about drug use in this study is based mainly on the most reliable information available, i.e. the daily methadone dosis, to which was added what was known about illicit drug use.

Table 3.4. Socioeconomic characteristics of the study groups (numbers and percentages).

		Study group n=187	Group 1 n=51	Group 2 n=47	Group 3 n=89
Documented accomodation	Good or reasonable accomodation	100 (54%)	43 (84%)	24 (51%)	33 (37%)
	Bad accomodation (bad sanitary and/or heating system, no gas or electricity, etc.	25 (13%)	2 (4%)	9 (19%)	14 (16%)
	Homeless	6 (3%)	0	0	6 (7%)
	Not known (not checked by social services or incomplete documentation in medical record)	56 (30%)	6 (12%)	14 (30%)	36 (40%)
Resources	Employment	6 (3%)	1 (2%)	3 (6%)	2 (2%)
	Unemployed with employed partner	11 (6%)	6 (12%)	1 (2%)	4 (4%)
	Unemployed benefit	148 (79%)	43 (84%)	42 (89%)	63 (71%)
	Financial support from parents	1 (0.5%)	1	0	0
	Not known	21 (11%)	0	1 (2%)	20 (23%)
Prostitution	Prostitution in present pregnancy	28 (15%)	4 (8%)	6 (13%)	18 (20%)
	Prostitution in history	39 (21%)	14 (27%)	14 (30%)	11 (12%)
Legal situation of previous children	Living with mother	21 (11%)	7 (14%)	5 (11%)	9 (10%)
	Father has custody over child(ren)	2 (1%)	0	0	2 (2%)
	Grandparents have custody over child(ren)	5 (3%)	0	1 (2%)	4 (4%)
	Foster care: mother lost custody	8 (4%)	0	2 (4%)	6 (7%)
	Foster care: mother renounced parenthood	2 (1%)	0	0	2 (2%)
	Foster care: child(ren) in foster care while mother did not lose custody	19 (10%)	1 (2%)	6 (13%)	12 (13%)
	No children	119 (64%)	39 (76%)	31 (66%)	49 (55%)
	Not known	11 (6%)	4 (8%)	2 (4%)	5 (6%)
(Psychosocial) Socioeconomic support from drug or social community services	Support received	139 (74%)	40 (78%)	42 (89%)	57 (64%)
	No support	41 (22%)	9 (18%)	5 (11%)	27 (30%)
	Incomplete documentation	7 (4%)	2 (4%)	0	5 (6%)

The classification of the study group in three categories, dependent on the use of legally provided methadone and/or illicit drugs (in particular heroin and cocaine) provides an opportunity to differentiate between the course and outcome of pregnancy in women who stopped all drug use in pregnancy, those who stabilized on methadone, and those who continued their illicit drug use, with or without legal methadone.

This pragmatic approach, however, does not allow to exclude confounding factors related to route, frequency, duration, timing of use, maximum blood levels, and purity of the illicit drugs used.

The study group was dependent on opiates and/or cocaine. There were only a few pure heroin users, which is not surprising since the heroin epidemy characterized the sixties and seventies and was followed in the eighties by cocaine and polydrug use (opiate, cocaine, amphetamine, benzodiazepine, marijuana etc.). The number of cocaine users was probably underestimated in the period 1983-1988 because of insufficient awareness of the problem in that time. The majority (78%) of opiate dependent women were enrolled in a legal methadone programa with the aim to stop illicit opiate use. This aim was achieved in half of the study population; the other half continued using illicit drugs, in particular heroin and cocaine. Only a few women were temporarily or during the whole pregnancy admitted to a therapeutic community; all others were enrolled in an ambulatory methadone maintenance program. It is striking that in the polydrug group there was hardly any change in the dose of methadone and more than fifty percent of the women were kept on a low-dose of methadone, despite their known, frequent illicit drug use. This is contrary to the principle, laid down in the protocol, that in an opiate dependent patient the daily methadone dose should be increased until the withdrawal symptoms and the search for drugs are suppressed [5,128,149,206]. Apparently, this principle was not applied consistently in the pregnant polydrug dependent population. In addition, the half-life of methadone is shortened during pregnancy, which may necessitate an increase in the daily dose[12,66,128,165]. Also the fact that various life, family and legal custody issues raise the stress level of the drug dependent pregnant woman will often necesitate an increase in the dose of methadone if illicit drug use is to be reduced[128,207]. In conclusion, it might have been possible to stabilize at least part of the women in the polydrug group on methadone, if they had been given a higher daily dose. Failure of methadone substitution during pregnancy may have unfavorable obstetric, psychologic, social and sometimes, legal consequences for mother and infant (see

Chapter 2).

The observation that 27% of the women in the study group completely stopped drug use is proof that withdrawal from drugs can be accomplished during pregnancy. The fact that the proportion of drug dependent pregnant women who became clean doubled from 18% in the period 1983-1988 to 37% in 1989-1992 indicates that a consistent multidisciplinary approach (simultaneous drug, health and social care) provides support to attempts to withdraw and abstain from drugs. As shown by the study of Stimmel et al[191], people living in a family constellation are more likely to detoxify, and women are more prone to complete a methadone detoxification program than men. Nearly half the number of women who succeeded in stopping drug use during pregnancy were still clean 1-10 years after delivery, suggesting that, contrary to early reports[41,65,66,150] that advocate maintenance on methadone rather than detoxification, withdrawal from drugs during pregnancy may be not only possible, but may also last. However, it should be emphasized that these women were in a reasonable, stable socioeconomic situation and benefited from the support of community services.

Smoking and alcohol consumption are known confounding variables for pregnancy outcome[114]. They were both significantly more frequently reported in the study groups than in controls, but the available data did not allow quantification. Specific questions that could permit the identification of changes in a woman's tolerance to alcohol and that are considered more important in the identification of alcohol use in pregnancy than the quantity of alcoholic beverages consumed[37], were not asked systematically. This situation probably expresses a persisting oversight from the part of medical care providers in the identification of pregnant women with alcohol problems. Another explanation could be the relative young age (26.5 years) of the pregnant women enrolled in the study, an age at which alcoholism is not frequently diagnosed.

Since the majority of drug dependent people are known as severe smokers and the distribution of smokers was similar between the three study groups, it is unlikely that the quantity of cigarettes smoked would differ markedly between the drug dependent women. The influence of cigarette smoking on fetal growth and development would therefore not be expected to be markedly different between the three groups of drug dependent pregnant women.

A significantly greater proportion of pregnant addicts in groups 1 and 2 than in the

polydrug group had good or reasonable accomodation, financial safety through unemployment benefit, used support from community services, and reported less prostitution during pregnancy. A family constellation was sometimes reported in the first group (living with children, benefiting from support by partner or parents). When the socioeconomic characteristics of the study group and the course of their addiction in pregnancy are put together, it seems that the best results regarding stabilization or stop of drug use in pregnancy are obtained in nulliparous women, in the presence of reasonable socioeconomic conditions and acceptance of support provided by drug, social and health care institutions.

Chapter 4

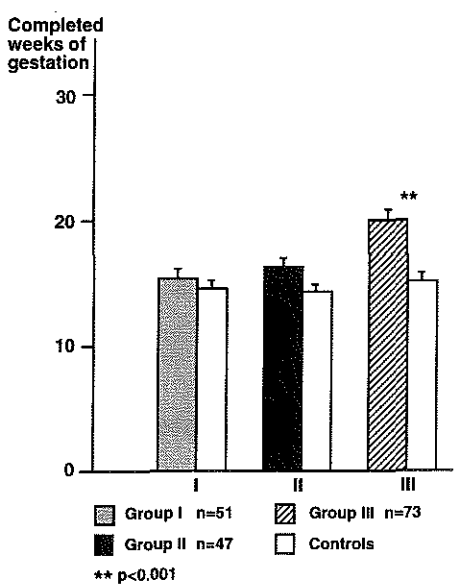
COURSE OF PREGNANCY

In this chapter obstetric data are presented concerning the course of pregnancy in drug dependent and control women.

4.1 General characteristics

Start of antenatal care

The mean gestational age at the first obstetric visit in the three groups of drug dependent pregnant women and their controls is shown in Fig 4.1.



There is no significant difference between the patients who became clean during pregnancy, the methadone-maintained women and their controls, although those using methadone (group 2) booked two weeks later than their controls ($p=0.04$), at 16 weeks gestation. The polydrug users who enrolled for antenatal care, started the obstetric visits at a mean of 21 weeks of pregnancy, 6 weeks later than controls ($p<0.0001$); 18% ($n=16$) booked for the first antenatal visit after 28 weeks gestation.

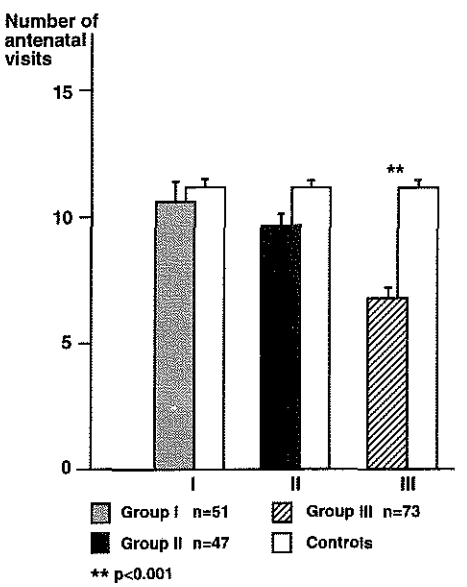
Fig.4.1 Mean gestational age (+ SEM) at the first obstetric visit in the three study groups and their controls.

All women in the first two groups of drug dependent pregnant women and controls were booked for antenatal care, but 18% of polydrug users were not booked before delivery. These cases were excluded from the statistical analysis of this particular subject.

Comparison of the mean gestational age at the first obstetric visit of drug dependent women in the two periods of 1983-1988 and 1989-1992 showed a small and nonsignificant difference between the first (18 weeks) and the second (16.5 weeks) period.

Participation in antenatal care

The mean number of antenatal visits of the three categories of drug dependent pregnant women in comparison with that of controls is shown in Fig 4.2.



Control pregnant women had significantly ($p<0.0001$) more obstetric visits (average 11) than drug dependent patients (average 8). The first two groups of drug dependent women had as many antenatal visits as their controls. The participation in the antenatal care program varied in poly-drug using women from no prenatal care to as many obstetric visits as the controls, with an average of seven visits for those who received antenatal care. This is significantly less than the average of 11 visits recorded in their controls ($p<0.0001$).

Fig.4.2 Mean number of antenatal visits (+ SEM) in the three study groups and their controls.

Eighteen percent (n=16) of polydrug users delivered without antenatal care and another 24% (n=21) had only one to four antenatal visits. Comparison of the two time periods of the study, 1983-1988 and 1989-1992, showed no difference with regard to the number of antenatal visits in drug dependent women and controls.

4.2 Complications of pregnancy

Infections

Both drug dependent and control populations were routinely screened in pregnancy for

syphilis and hepatitis B. A positive surface antigen (HbsAg) for hepatitis B was found in five of the 187 drug using pregnant women (2.7%) and in one control (0.5%), a nonsignificant difference. All patients with positive HbsAg were asymptomatic and had normal liver enzymes. The screening for hepatitis B showed that many drug dependent women had antibodies against the hepatitis B antigens. Of the drug addicted patients 15% had hepatitis B antibodies, significantly ($p<0.0001$) more than the 0.5% in controls. The difference remaines significant when the analysis is carried out within the subgroups. The third group recorded the highest number of drug dependent women with positive hepatitis B antibodies ($n=16$). Positive serologic tests indicating early or latent syphilis infection were present in 15% of the drug dependent women, significantly ($p<0.0001$) more than the 1.6% in the control group. Repetition of the syphilis screening in drug dependent women in the third trimester of pregnancy revealed one case of syphilis reinfection. Table 4.2 shows that the distribution of early and latent syphilis and/or hepatitis B carriers was similar in the three groups of drug dependent pregnant women.

After 1985 all pregnant women were offered screening for HIV infection; of 140 patients three refused to be tested. In the drug dependent population four women tested positive for HIV, compared to none in the control group (Table 4.1).

Table 4.1 Number and type of infections in the study and control groups.

Type of infection	Study group n=187	Control group n=187
Screened		
Early syphilis	5	1
Latent syphilis	23	2
Hepatitis B carriers	5	1
HIV seropositivity	4 ■	0 ■
Neisseria gonorrhea (acute)	7	1
Not screened		
Chlamydia trachomatis	1	0
Condilomata accuminata	2	0
Urinary tract infections	15	3
Trichomonas vaginalis	22	1
Candida albicans	5	2
Pediculosis pubis	1	0
Impetigo vulgaris	1	0

■ n=137

Table 4.2 Distribution of early and latent syphilis and hepatitis B carriers in the 3 groups of drug dependent women and their controls (numbers).

Type of infection	Group 1 n=51	Group 2 n=47	Group 3 n=89	Control Group 1 n=51	Control Group 2 n=47	Control Group 3 n=89	Study population n=187	Control population n=187
Early syphilis	0	2	3	0	0	1	5	1
Latent syphilis	7	4	12	0	1	1	23	2
Hepatitis B carrier (HbsAg+)	3	1	1	0	1	0	5	1
Positive hepatitis B antibodies	4	8	16	1	0	2	28	3

All four were white, Dutch, of low socioeconomic status, with poor education, and addicted to opiates since more than 5 years. Family support, represented by parental support or a stable partner relationship during pregnancy was present in three of the four cases. All HIV-seropositive women had used heroin intravenously and had a history of multiple infections (pneumonia, multiple lung abcesses, endocarditis, hepatitis B, staphylococus sepsis with arthritis), prostitution and sexually transmitted diseases; sexual abuse and violence were present in all cases. One of the women had an impaired T4/T8 lymphocyte ratio, and another had mild thrombocytopenia, but the abnormal indices did not progress and none of the women developed AIDS during pregnancy. Despite counselling, the four women did not opt for abortion; one infant is known to have developed AIDS. Two of the women were aware of the fact that they were HIV positive and became pregnant intentionally, despite information and counselling about the risks of pregnancy associated with HIV infection. They had both monogamous relationships with drug free, HIV-seronegative partners. Two HIV positive patients reduced and one of them stopped drug use after they knew they were pregnant. A third woman is known to have stopped drug use but to have increased her benzodiazepine and alcohol consumption. The fourth patient, with a long history of a variety of sexually transmitted diseases, continued street prostitution during pregnancy. This HIV seropositive woman used a large intravenous dose of heroin in addition to diazepam, rohypnol, alcohol and nicotine and she continued her lifestyle throughout pregnancy. The course of pregnancy was uneventful in three HIV-seropositive patients; the fourth woman required treatment for a syphilis reinfection during pregnancy and cystitis. The partners of two other drug dependent pregnant women were

known to be seropositive for HIV; the pregnant women themselves, and later their infants, remained seronegative during pregnancy and were still negative at postpartum checkup. The data summarized in Table 4.2 show that gonorrhea was detected in 4% of the drug using patients, compared with only one control woman. During the ten years period of the study, a regional screening program for infection with toxoplasma gondii was carried out, and 71 patients of the study population were screened for toxoplasmosis; none of them appeared to be infected. Signs and symptoms of urinary infection were frequent in the drug dependent group: 15 cases in 187 drug addicted women as compared with only three in the control group. Seven of the 15 cases of urinary infections occurred in the polydrug using group. There were two cases of pyelitis in the study group versus none in the control population. However, urine cultures remained sterile in all but two cases of pyelitis. Except for trichomonas vaginalis, which was found in 12% of the drug dependent women, other types of infections were diagnosed sporadically. Impetigo vulgaris appeared on the limbs of a polydrug dependent patient with extensive scratch effects after daily high dose cocaine use.

Hospitalization

The main reasons for hospitalization during pregnancy in the study group as well as in controls were threatened preterm labor, fetal growth retardation, and preterm rupture of membranes. Table 4.3 shows the distribution of complications in pregnancy in the drug dependent women and their controls.

Table 4.3 Summary of the obstetric pathology in the study and control groups (numbers).

Obstetric pathology	Study group n=187	Control group n=187
Threatened preterm labor	25	14
(Preterm) rupture of membranes	9	9
Fetal growth retardation	16	2
Antepartum hemorrhage	2	1
Pregnancy-induced hypertension	1	5
Preeclampsia	1	2
Pregnancy-induced diabetes	0	3

Threatened preterm labor was reason for hospital admission in 13% of drug addicted women in comparison with 7% in controls, a nonsignificant difference. The highest percentage (16%) of admissions for threatened preterm labor (n=14) was recorded in the group of polydrug users (n=89) compared with nearly 3% (n=5) in their control group, but also this difference is not significant at the one percent level (p=0.04); the polydrug abusers were responsible for more than half (n=14) of all admissions for threatened preterm labor in the study population.

Suspicion of fetal growth retardation was significantly more often ($p < 0.001$) reason for hospitalization in drug dependent pregnant women (9%) than in their controls (1%); the relative risk of hospitalization because of fetal growth retardation in drug dependent women was 8 (95% CI: 2-34). More than half of the recorded hospitalizations due to inappropriate fetal growth belonged to the polydrug dependent group (n=10).

The occurrence of antepartum hemorrhage was not different between drug dependent women and controls. Two drug addicted women developed abruptio placentae; one occurred at 28 weeks of gestation following the use of a high dose of cocaine; the second one occurred at term in a patient who had withdrawn from antenatal care. Cesarean section was succesfully performed in both patients, resulting in liveborn infants. None of the control patients had abruptio placentae. One case of complete placenta previa was recorded in the control group, and the pregnancy was terminated successfully by cesarean section. Hypertensive disorders, and pregnancy-induced diabetes were more often responsible for hospital admission in the control group than in the drug dependent patients, but the numbers are small. There were no cases of hospital admission because of anemia, hemoglobinopathies or other hematologic diseases. None of the drug addicted pregnant women or controls was admitted because of malnutrition or vitamine deficiency.

4.3 Discussion

Various studies have shown that, in the absence of a supportive program, prenatal care is usually poor in pregnant addicts[41,124,161,213]. The results of other studies, in particular after 1985, have indicated that improvement in the outcome of pregnancies associated with drug use is possible when comprehensive antenatal care is provided[22,69,105,150,166,193]. The Rotterdam multidisciplinary approach aimed at early referral and booking of pregnant addicts for antenatal care. The mean gestational age at booking of the control group was

14 weeks, only two weeks earlier than that in the clean and methadone groups; this indicates that for these women one of the goals of the program was reached. Social conditions were better in the clean and methadone groups, and the women cooperated better with drug, health and social care services than polydrug using women.

Of the polydrug addicts of group 3, 24% had no antenatal care at all, and the women who were booked started antenatal care approximately 6 weeks later and used the facilities much less frequently than controls and than drug dependent women belonging to the first two groups. This group of illicit drug users often avoided contacts with community services and health care institutions,and their living conditions were usually poor. The results obtained in this group with regard to the start of obstetric visits and the participation in the antenatal care program are in agreement with those reported in the literature[59,60,96]. It may be possible to improve the antenatal care for these pregnant women by more careful evaluation of their condition, and by increasing their methadone dose until the withdrawal symptoms and the search for drugs are suppressed. As discussed in chapter 2, the principle of the lowest effective dose of methadone, rather than the lowest possible dose, was not always adhered to, which may be partially responsible for the continuing drug seeking behavior and missing antenatal visits in this group of women.

Pregnant addicts are considered at high risk of sexually transmitted diseases and systemic or local infections[61,92,93,95,189,200,201,208], which is confirmed by the results of this study. Although the number of hepatitis B carriers was similar in study patients and controls, the number of infected pregnant addicts who developed anti-HBs (15%) is threefold higher than expected in a general population (5%) and nine-fold higher than in own controls (1.6%). This confirms the high risk of hepatitis B infection in drug dependent populations. The patients were not screened for hepatitis C and D. Recent studies[95,180,200,201] emphasize the importance of maternal hepatitis C seropositivity with regard to the vertical transmission of the virus and its frequent co-existence with other infections, such as HIV and sexually transmitted diseases. Intravenous drug use is the most commonly identified risk factor for hepatitis C infection[61,95,180]. The lack of solid data with regard to the management of hepatitis C or D seropositive newborns complicates the issue [200]. What is needed is a prospective study that follows infants born to hepatitis C seropositive but HIV seronegative mothers in order to establish determinants of vertical transmission and to develop recommendations for clinical management.

Only few of the studies concerning drug dependency in pregnancy present the incidence of syphilis and, in general, the occurrence of primary or secondary syphilis is not specified[41,192]. We found infection with Treponema pallidum in 15% of drug dependent pregnant women, an incidence similar to that reported by Stone et al[192] (17% in 378 drug dependent pregnant women) and Connaughton et al[41] (20% in 278 drug dependent pregnant women). However, the diagnosis of syphilis in drug dependent pregnant women, in particular in those who are also HIV-seropositive, should be made with caution because of the possibility of false-positive serologic reactions[175]. The diagnostic method applied in this study, consisting of VDRL and TPHA fixation in fresh sera, followed by FTA-ABS determination in case one of the first two tests was dubious or positive, offers a specificity of 98.7% - 100% for diagnosing a Treponema pallidum infection[91]. Longitudinal assessment of the serology was performed in all positive or dubious cases, but this was not clinically relevant because uncertainty was resolved by treatment. The significantly elevated incidence of syphilis in drug dependent women can be understood from their history of prostitution and multiple sexually transmitted diseases. There is a risk of reinfection during pregnancy (one seroconversion was recorded in the study population), which justifies the repetition of syphilis screening in late pregnancy[91,132].

The proportion of HIV-seropositive pregnant patients was low (2%). The proportion of HIV-seropositive pregnant addicts may be expected to be lower than the proportion of HIV-infected drug dependent women in the general population for two main reasons[145]. First, although no data on the fertility of HIV-seropositive drug addicted women are available, it seems likely that fertility is reduced because of the negative effects of drug abuse on general health, nutrition, and living conditions, and the increased incidence of genital infections. Second, contraception and abortion are used by HIV-seropositive women who want to avoid pregnancy. In case of a negative HIV-test, retesting of the pregnant addict should be considered before delivery in order to detect seroconversion. No effects of pregnancy on the progression of HIV-infection and no antepartum obstetrical complications were observed in the HIV-seropositive pregnant addicts; although the number was small, this finding is in agreement with those reported by Lindsay SA et al[122] in pregnant HIV-infected patients. At the first obstetric visit attention should be payed to the partner of a drug dependent woman, since many of them are also addicts and they represent a high-risk group for HIV-infection[4,122]. An HIV test should be offered to the partners of drug addicted

pregnant women, especially when they admit using or having used drugs intravenously. The low incidence of demonstrated Chlamydia infection in the presence of a high proportion of drug dependent women treated for urinary infections is remarkable. Chlamydiae are known to produce lesions of transitional cell epithelium, which may result in dysuria and frequent micturition. In the presence of these signs in a woman known to use drugs, who belongs to the risk group for Chlamydia infection, a Chlamydia trachomatis culture or a direct-slide fluorescence-tagged Chlamydia monoclonal antibody test is mandatory[93,189]. None of the many patients with urinary symptoms and a sterile urine culture in this study was tested for Chlamydia infection and it may well be possible that the number of Chlamydia infections has in fact been much larger than the only case that was found. We agree with the present recommendation to routinely screen drug dependent pregnant women for Chlamydia infection[101] so that appropriate treatment can be instituted. In agreement with the literature[41,100,104], the most frequent antepartum complications in the study group were inadequate fetal growth and threatened preterm birth, in particular in the polydrug using pregnant women. A definitive diagnosis of fetal growth retardation can only be made after birth and, as will be discussed in chapter 5, fetal growth retardation occurred indeed significantly more frequently in polydrug using women. In this study 81% of the pregnant addicts continued smoking in pregnancy, compared with 23% smokers in the control population. In combination with drug abuse, smoking and alcohol abuse during pregnancy are known to increase the incidence of inadequate fetal growth[72,125,136,166,205]. Preterm labor was also a more frequent reason for hospital admission in the drug dependent population than in controls, and again the polydrug abusers were responsible for the highest number of admissions. Recent studies from the U.S.A.[151] recommend to subject all patients admitted with threatened preterm labor to screening for substance abuse. Indeed, in our study two women tested positive and admitted drug use only after admission because of threatened preterm labor. However, because the prevalence of drug abuse in the Dutch population of pregnant women is not known but may be low, it is questionable if standard screening for drug abuse should be implemented in all pregnant women admitted for threatened preterm labor in this country. The important question whether preterm labor is a pharmacologic result of drug use or if it is due to other factors, e.g. infections and stressful life events associated with drug dependence, remains to be answered and will be discussed in more detail in chapter 5.

The illicit polydrug abusers were responsible for the highest proportion of hospital admissions. One explanation is that these women often present for obstetric care only when something is wrong, and immediate hospitalization is necessary. Also, the obstetric care provider may be inclined to hospitalize polydrug dependent pregnant women earlier, because they may not return for evaluation. Sometimes the obstetric complication may be linked directly to illicit drug use, as in our two cases of abruptio placentae recorded after cocaine use[2,85,164,182]. With regard to hypertensive disorders in pregnancy, our results confirm those of other studies[115,193], which also failed to demonstrate a significant difference in the occurence of pregnancy-induced hypertension and preeclampsia between drug abusing and drug-free pregnant women. This finding is also valid for cocaine users, although cocaine is known to produce transient hypertension[74,164,182,211]. Some investigators[41,192] reported an elevated incidence of hypertensive disorders in pregnant narcotic addicts. The results of the studies are questionable because diagnostic criteria were not defined. There is also no pathophysiologic explanation as to why hypertensive disorders would occur more frequently in drug dependent than in drug free pregnant women.

Chapter 5

DELIVERY AND THE NEWBORN

Data about delivery, condition and size of the infant at birth are presented in this chapter together with data on the neonatal withdrawal syndrome and neonatal deaths in the study group and controls. Pediatric morbidity was not subject of this study.

5.1 Delivery

Gestational age

The mean week of gestational age at delivery in the three groups of drug dependent patients and their controls is shown in Fig 5.1.

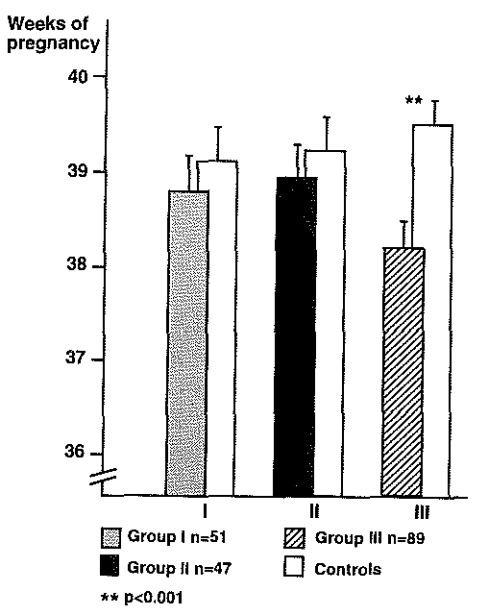


Fig.5.1 Mean gestational age (+ SEM) at delivery in the three study groups and their controls.

The majority of the women in all groups were delivered after 37 weeks gestation. There is no significant difference between the first two drug dependent groups and their controls; they all delivered at about 39 weeks of pregnancy. The women in the polydrug group were on the average delivered at 38 weeks, about two weeks earlier than their controls. Although this difference is statistically significant ($p<0.0001$), it is clinically irrelevant.

Of the drug dependent mothers 20% delivered preterm, compared with 9% of controls ($p=0.002$). In both study control populations the majority of preterm births occurred after 34 weeks of

pregnancy; only nine drug dependent women delivered before achieving 34 weeks of gestation compared with eight cases in the control population. Three early preterm deliveries in drug dependent women (at 25 and 28 weeks, respectively) were associated with consumption of large amounts of drugs, in particular cocaine, or with acute drug withdrawal (27 weeks of gestation). In the control group only one delivery occurred before a gestational age of 30 weeks, because of prolaps of the umbilical cord. Of the 16 drug dependent pregnant women without antenatal care, three delivered preterm (34-36 completed weeks of pregnancy). The effects of drug use in pregnancy on preterm delivery expressed in odd ratios with their confidence intervals are shown in Fig 5.2. The likelihood of a preterm delivery in groups 1 and 2 is not different from that in controls, but the odds ratio in group 3 is significantly increased. The odds ratio of 6.6 in favor of preterm delivery in drug using women in group 3 is responsible for the total odds ratio of preterm delivery of 2.5 (95% CI 1.9-4.7). The relative number of preterm births recorded in the periods 1983-1988 and 1989-1992 was similar in drug dependent pregnant women (17/93 cases versus 21/94) and the same was true for the controls (8/93 and 9/94 cases, respectivly).

There were no significant differences in mean placental weight between study patients and controls (569g vs 613g). Of the 96 placentas of drug dependent women that were histologically examined, ten showed placental infarcts, compared with four of 99 controls, a nonsignificant difference.

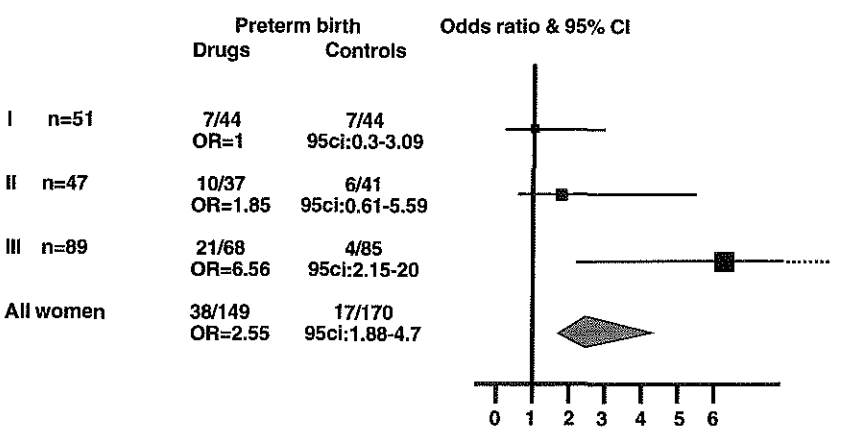


Fig.5.2 Preterm birth in drug dependent pregnant women and controls (odd ratios & 95% CI).

Complications

Information about the mode of delivery and the occurrence of meconium stained amniotic fluid is presented in Table 5.1. The incidence of spontaneous and operative deliveries was similar in drug dependent and in control groups. Although the incidence of cesarean section was similar in the study group (n=14) and controls (n=16), the indications to perform it were different in the two populations. The main reason to perform a cesarean section in pregnant addicts was fetal distress revealed by the cardiotokogram. In the control population the indications for cesarean section were more variable: in addition to fetal distress (n=5), they included protracted labor (n=3), abnormal presentation (n=3), repeat cesarean section (n=3), placenta previa (n=1), and prolaps of the umbilical cord (n=1).

5.2 The newborn

Condition at birth

No significant differences were demonstrated between the Apgar scores of the infants born to addicted or nonaddicted mothers (Table 5.1). Umbilical arterial acid-base values could not be used to assess neonatal condition in the various groups, because they were not routinely determined. The difference with regard to the occurrence of meconium stained amniotic fluid in drug addicted patients (25%) compared with controls (15%), is not statistically significant. No cases of meconium aspiration were observed.

Birthweight and birthweight ratio

Values of weight, length and head circumference at birth, and their ratios, are presented in Table 5.2. No significant differences were observed between the birthweights in the "clean" group and in controls. In group 2, the median birthweight was 400 g lower ($p < 0.001$), and in group 3, it was 600 g lower than that in controls ($p < 0.001$). Infants born to polydrug dependent mothers without antenatal care (n=16) had mean and median birthweights similar to the rest of the third group; the differences are represented graphically in Fig 5.3. The birthweight ratios show a similar tendency. All controls had birthweight ratios of approximately 1, indicating normal fetal growth. In group 1 the birthweight ratio of 0.97 is somewhat below that in controls, but the difference is not significant, whereas birthweight ratios in the second and third study group are approximately 12 % lower than those in controls ($p < 0.001$).

Table 5.1 Mode of delivery, aspect of amniotic fluid, and Apgar-scores in the study and control groups (numbers).

Variables related to delivery	Study group n=187			Control group n=187		
	Group 1 n=51	Group 2 n=47	Group 3 n=89	Control 1 n=51	Control 2 n=47	Control 3 n=89
Spontaneous delivery (head or breech presentation)	46	35	72	35	39	73
Cesarean section	2	4	8	5	4	7
Operative obstetrics (forceps or vacuum extraction)	7	9	9	10	4	9
Meconium stained amniotic fluid	17	10	21	7	10	11
Apgar at 1 min. ≤ 7	6	6	13	4	7	10
Apgar at 5 min. ≤ 7	1	0	3	2	2	0

Table 5.2 Variables of fetal growth in the three study groups and their controls (medians, range).

Size at birth	Group 1 n=51	Drug-dependent women median (min-max)	Controls median (min-max)	Significance
Birth weight (g)		3180 (640 -3805)	3335 (1035-4230)	NS
Birth length (cm)		49 (32 - 54)	50 (44 - 54)	NS
Head circumference (cm)		34 (30 -35.5)	34 (30 - 38)	NS
Weight ratio		0.97 (0.62-1.20)	1 (0.54-1.33)	NS
Length ratio		0.97 (0.88-1.07)	0.98 (0.90-1.1)	NS
Head circumference ratio		0.97 (0.90-1.05)	0.99 (0.91-1.12)	NS
	Group 2 n=47			
Birth weight (g)		2970 (1070-4245)	3370 (1035-4400)	**
Birth length (cm)		48 (40.5- 53)	50 (44.3-53.5)	**
Head circumference (cm)		33.5 (30 - 36)	34.5 (30.5- 39)	*
Weight ratio		0.92 (0.58-1.21)	1.05 (0.61-1.31)	**
Lenght ratio		0.97 (0.85-1.07)	1 (0.92-1.05)	**
Head circumference ratio		0.98 (0.87-1.03)	1.01 (0.90-1.11)	*
	Group 3 n=89			
Birth weight (g)		2805 (715 -3690)	3380 (925 -4915)	**
Birth lenght (cm)		48 (43 - 52)	50 (34.5- 55)	**
Head circumference (cm)		33 (29 - 37)	34 (26 - 39)	**
Weight ratio		0.89 (0.62-1.25)	1 (0.54-1.41)	**
Length ratio		0.96 (0.85-1.07)	0.99 (0.83-1.08)	**
Head circumference ratio		0.99 (0.87-1.07)	0.99 (0.88-1.11)	NS

Values expressed as median (min-max). * $p < 0.01$; ** $p < 0.001$; NS = not significant

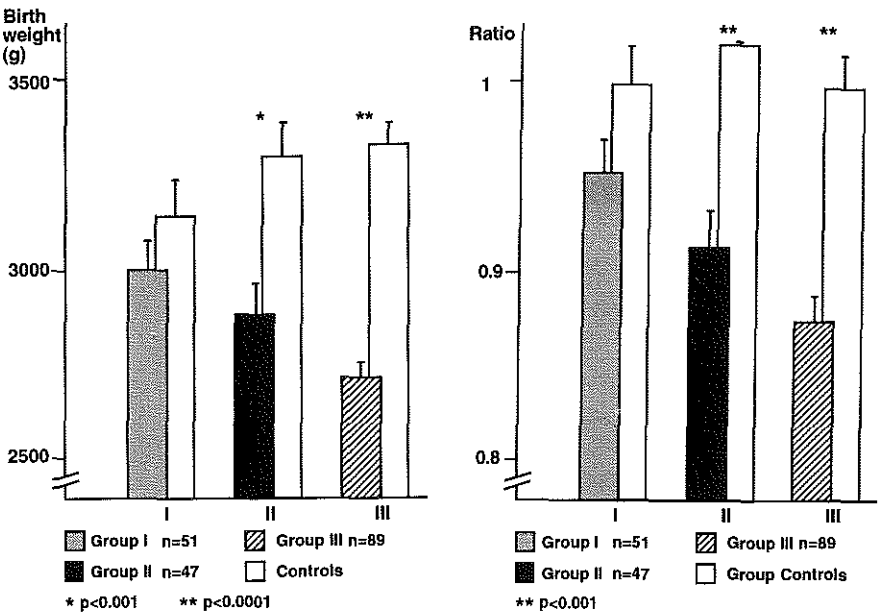


Fig.5.3 Mean birth weight (+ SEM) (left) and birthweight ratios (+ SEM) (right) in the study and control groups.

Nineteen percent (95% CI: 14-25) of the 187 babies born to drug dependent mothers were small-for-gestational age, significantly more than the 9% in controls (95% CI: 5-13%). Five of the 16 drug dependent pregnant women who did not receive antenatal care delivered infants who were small-for-gestational age and two of them were very small-for-gestational age (< P 2.3). For the total study group this means that 6% of the infants born to drug dependent mothers were very small-for-gestational age (95% CI: 3-9) compared with only 3% in controls (95% CI: 1-6). The likelihood of being born with a weight beneath the 10th percentile of the reference curve in group 1 was equal to that of controls, but it showed a significant increase in groups 2 and 3 (Fig.5.4). In groups 2 and 3 the odds ratios were significantly elevated and responsible for the total odds ratio of small-for-gestational age infants of 2.4.

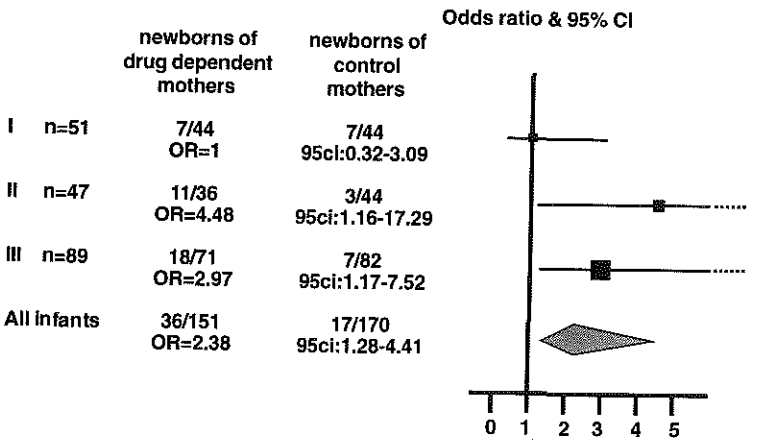


Fig.5.4 Small and very small-for-gestational age newborns in the study and control groups (odds ratios and 95% CI).

Length and length ratio

Length and length ratios show the same pattern as that observed concerning birthweight (Fig. 5.5).

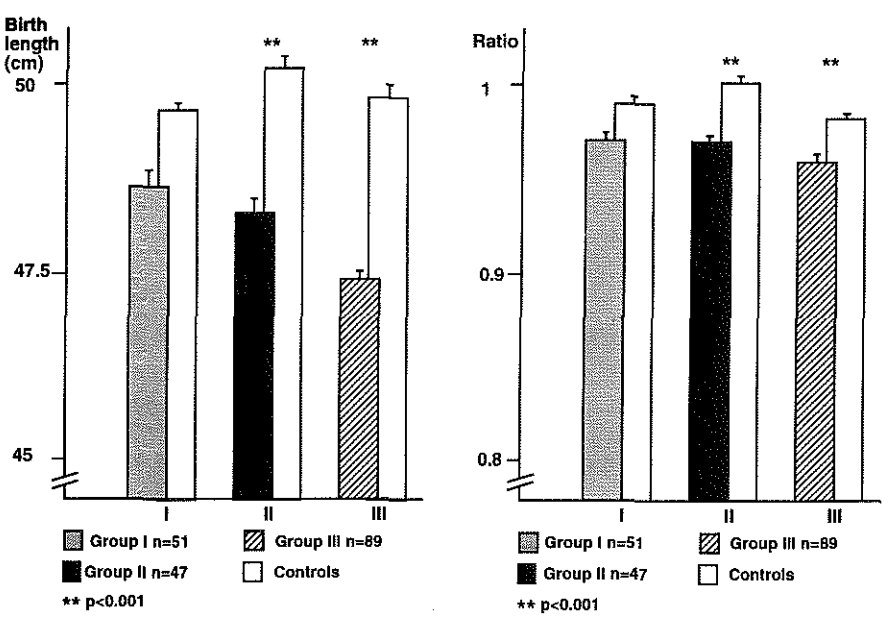


Fig.5.5 Mean length (+ SEM), left, and mean length ratios (+ SEM), right in the study and control groups.

No difference was demonstrated between the length and length ratio of infants born to control mothers and to mothers of group 1 who stopped all drug use in pregnancy. However, infants in the study groups 2 and 3 were on average 2 cm shorter and had a median length ratio that was 3% less than that of infants in the control groups ($p < 0.001$). The same is true for the infants whose mothers withdrew from antenatal care.

Head circumference and head circumference ratio

Values of head circumference and head circumference ratios of drug dependent pregnant women and controls are graphically presented in Figure 5.6.

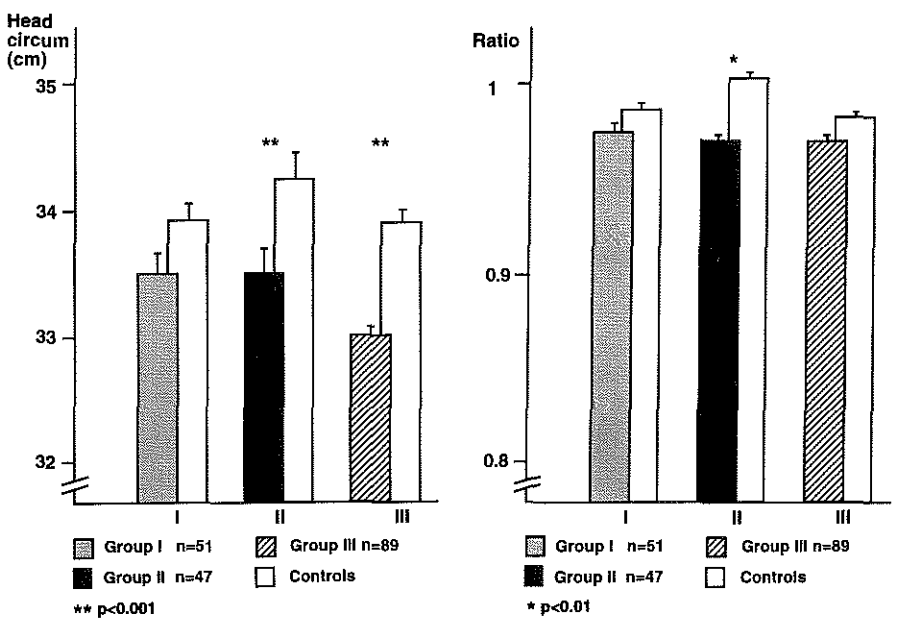


Fig.5.6 Mean head circumference (+ SEM), left, and mean head circumference ratios (+ SEM), right in the study and control groups.

The mean head circumference of the infants born to the methadone (group 2) and polydrug dependent mothers (group 3) was 1 cm less than that of control infants ($p < 0.001$) and the head circumference ratio was approximately 2% smaller ($p < 0.01$) than that in controls. Drug dependent infants born after an uncontrolled pregnancy had a similar outcome concerning head and head-circumference ratio as the rest of infants born to drug

dependent mothers.

When the ratios of weight, length and head circumference are considered together as a measure of fetal growth, it appears that infants born to control and group 1 mothers show appropriate growth, with three equivalent ratios. The ratios of weight, length and head circumference of infants born to mothers in the second and third group of drug dependent patients are proportionally reduced in comparison with their controls, indicating proportional retardation of fetal growth.

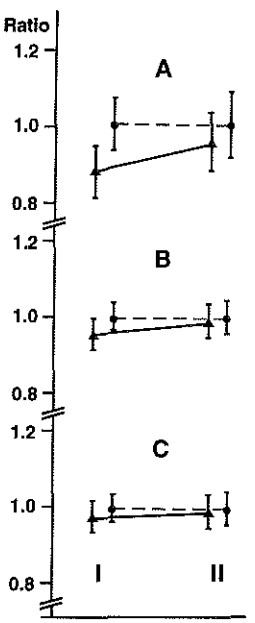


Table 5.3 and Fig 5.7 show the variables of fetal growth in the study population and controls in the periods 1983-1988 and 1989-1992 of the study. While the size of infants born to control mothers remained the same in the two periods, the intrauterine growth of infants born to drug dependent women appears to have been significantly better in the last than in the first period; in the second period the infants were nearly 250 g heavier and 1.5 cm longer ($p < 0.001$).

Fig.5.7 Fetal growth, expressed in growth ratios (from top to bottom: weight, length and head circumference ratios) in the study (△) and control (●) groups in the periods 1983-1988 (1) and 1989-1992 (2).

Congenital anomalies

Six cases of fetal anomalies were recorded in the study population versus none in controls. All anomalies occurred in women who continued their drug use during pregnancy, none were found in the clean group. During the ten years study period, 86% of drug dependent patients (n=160) underwent a special ultrasound examination to detect fetal anomalies. Two cases of severe congenital malformations were diagnosed during pregnancy by ultrasound. Both mothers received obstetric, pediatric and genetic counselling and decided to continue their pregnancy. One male infant was born at term with an atrial septum defect, esophagus atresia and hypospadia, and was successfully operated.

Table 5.3 Variables of fetal growth in the study and control groups in the period 1983-1988 and 1989-1992.

Variables of growth	Period 1983-1988 n=93				Period 1989-1992 n=94			
	Drug-dependent mothers		Control mothers		Drug-dependent mothers		Control mothers	
	Median	(Min-Mx)	Median	(Min-Mx)	Median	(Min-Mx)	Median	(Min-Mx)
Birth weight (g)	2760	(640-3805)*†	3345	(1200-4915)	3012.5	(715 -4245)*	3377	(925 -4400)
Birth length (cm)	47.5	(32 - 54)*†	50	(44 -55.5)	49	(43 - 53)*	50	(35.5- 54)
Head circumference (cm)	33	(29 - 37)	34	(30 - 39)	33.5	(30 - 36)	34	(27 - 39)

* p < 0.001 vs controls † < 0.001 vs drug dependent women in period 1989-1992.

His mother had been using methadone and heroin during pregnancy. A female infant was born at 34 weeks of pregnancy with agenesis of the right foot and left hand. The mother had been taking large amounts of cocaine around the time of conception and in the first trimester of pregnancy. In a depressive mood, she started using heroin at 34 weeks and went into preterm labor. Both mothers received intensive medical and psychosocial support and care. One of them succeeded in stopping drug use after delivery, the other one was able to reduce and stabilize the amount of drugs taken; both received custody over their infants. One of the mothers had delivered three times before and had never succeeded in controlling her drug dependency and keeping custody over her previous infants. One severe heart malformation was detected after birth. The heroin dependent mother had attended the antenatal clinic sporadically, and she had not kept her appointments for ultrasound screening. The infant was born with a hypoplastic aorta and a ventricular septum defect, and died after 5 weeks.

Minor malformations were diagnosed in three infants of drug dependent mothers concerning two cases of polydactyly and syndactyly and one case of a double left ear.

Neonatal withdrawal syndrome

None of the newborns of mothers of the clean group (group 1) showed signs of withdrawal. All infants born to the 136 drug dependent mothers who continued drug use during pregnancy were susceptible to developing a neonatal withdrawal syndrome within hours or days after birth. Twenty-three of those newborns were referred to neonatal units in other hospitals, in the Netherlands or even abroad, because at the time of birth no neonatal beds were available in our hospital. Documentation about the absence or presence and severity of the neonatal withdrawal syndrome was not available or incomplete in those neonates who belonged to the methadone (n=4) and polydrug groups (n=19). Of the infants of the methadone group 57% (n=27) and 70% of those born to polydrug using mothers (n=62) were treated with phenobarbital (n=87) or paregoric (n=2). Paregoric (Tinctura opii camphorata with 0.4mg/ml morphine) was used only in cases with an insufficient response to phenobarbital. From the other 18 infants, six (two from the methadone and four from the polydrug group) developed mild signs of neonatal withdrawal syndrome and adequate nursing was sufficient. No clear signs of neonatal withdrawal syndrome developed in 14 infants born in the methadone group and four newborns born to polydrug using mothers during a hospitalization period of at least 12 days. Many infants born to drug addicted mothers required prolonged hospitalization after their mothers' discharge, 12% in group 1, 77% in group 2, and 80% in group 3. Neonatal withdrawal syndrome was a frequent indication for the hospitalization of these infants, but prematurity, inappropriate growth, and protracted jaundice were other reasons, in addition to socioeconomic problems and awaiting decisions to be taken on the basis of the final report of Central Address.

Perinatal mortality

One fetal death occurred in the drug addicted group, compared with none in the controls. The pregnant woman with fetal death was treated in a therapeutic community and her methadone dose had been reduced from 70 mg daily to zero in 5 weeks. Fetal growth retardation was diagnosed at 27 weeks gestation and she was referred for clinical observation and bed rest. Immediately after admission the fetal cardiotokogram showed signs of severe fetal distress, suggestive of a dying fetus. Because fetal weight was estimated at 500-600 g, the presence of hypoxic and acidotic brain damage was likely, and chances of survival were considered minimal, no action was undertaken. Fetal death

occurred one day later, and she was delivered of an extremely growth retarded 640 g fetus, without congenital abnormalities. Histologic examination of the placenta, chromosome investigation of the infant and maternal laboratory tests, including lupus anticoagulant and anticardiolipin-antibodies, were unremarkable.

No neonatal death was recorded in the control group. In the drug dependent group one neonatal death occurred two days after birth as a consequence of severe prematurity in an infant born at 25 weeks gestation. The preterm delivery was preceded by consumption of large amounts of cocaine and heroin. A few months after this preterm delivery the woman was booked for antenatal care with a new pregnancy. This time she took part in a methadone program, tried to control her illicit drug use and followed the guidelines of the antenatal care program; this second pregnancy was uneventful and resulted in the birth of a healthy infant at 39 weeks gestation.

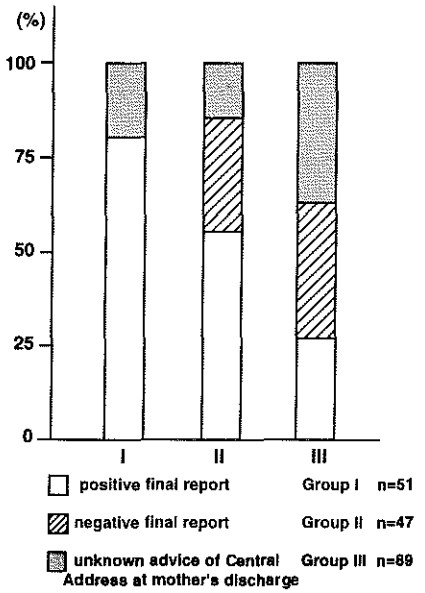
No deaths in the first year of life were documented in the control group, whereas four infants born to drug dependent mothers died. Three of the infants were born at term in good health, with a normal birthweight; they died unexpectedly at the age of 5 weeks, 2 and 7 months, respectively, in the absence of any preceding illness. The mother of one of the infants was HIV seropositive. Postmortem examination revealed no cause of death and a tentative diagnosis of Sudden Infant Death Syndrome (SIDS) was made. A fourth child died 35 days after birth because of congenital hypoplasia of the aorta and a ventricular septum defect. The mother had used heroin throughout pregnancy and had received poor antenatal care.

One case of pediatric AIDS was recorded in the study group. The signs of the disease developed at the age of four months and the infant succumbed one year later.

Final psychosocial report

The final report of Central Address was of importance for the discharge of an infant born to a drug dependent mother.

Fig 5.8 presents the distribution of positive, negative or unknown final psychosocial reports in the three groups of the study population. The distribution is in agreement with the women's drug behavior, socioeconomic conditions and participation in the comprehensive antenatal program.



No negative final report was brought out in the first group compared with 30% and 46%, respectively, negative reports recorded in the methadone and polydrug dependent groups. In the third group the final number of negative reports is probably much higher since in 37% of the cases no decision had yet been taken at the time of the mother's discharge.

Fig. 5.8 The distribution of positive, negative or undecided final reports in the three study groups.

In the period 1989-1992 the work of Central Address resulted in more definitive positive (55%) or negative (32%) advices and less cases with undecided reports (13%) at the time of postpartum discharge than in the preceeding period. In the period 1989-1992 the number of drug dependent women who abstained from drugs during pregnancy was twice that in the period 1983-1988 (see also Chapter 3).

The distribution of the final reports in the study population during the two periods is presented in Fig. 5.9.

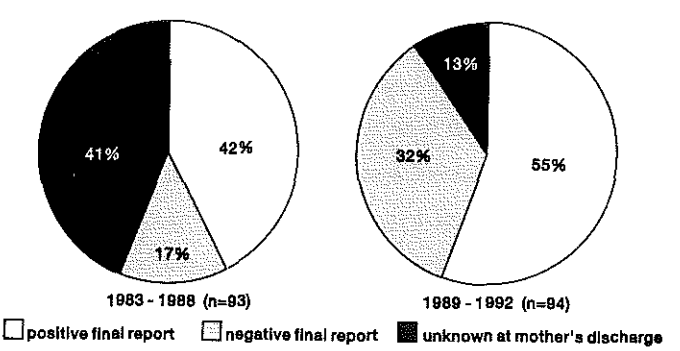


Fig.5.9 Final reports in the periods 1983-1988 and 1989-1992.

5.3 Discussion

Elevated rates of prematurity, low birthweight, and neonatal morbidity and mortality were observed in infants born to drug dependent mothers.

The mean gestational age at delivery in the study group of 38.5 weeks is similar to that reported in previous studies of pregnancies complicated by opiate use[31,25,193]. In contrast to the gestational age at delivery of the women who terminated (group 1) or reduced (group 2) their drug use, which was equal to that in controls, the mean gestational age at delivery in study group 3 of women with polydrug use was significantely reduced because of a higher prematurity rate. This observation is in agreement with earlier findings [81,105,125]. The results of the present study show clearly that continuous use of opiates during pregnancy, usually in combination with cocaine and associated with prostitution, infections (in particular sexually transmitted diseases), poor socioeconomic conditions, stress, lack of psychosocial support and deficient antenatal care (group 3), increases the likelihood of preterm delivery about sixfold compared with controls and with women who terminated their drug use in pregnancy. Our results are in agreement with those of controlled [41,193] and uncontrolled[89,96,159] studies that reported a higher average incidence of prematurity in heroin users (28%) compared to that in women using methadone (14.9%). The published data on prematurity is even more solid in cocaine studies[80,148,215]. Controlled cocaine studies found significantly increased rates of preterm deliveries in cocaine using populations compared to controls[24,28,80,109,125,129,148].

The question whether preterm labor is a direct consequence of drug use, or if its higher rate in a drug dependent population is due to other factors, cannot be answered easily. The pharmacologic properties of opiates do not explain the occurrence of uterine contractility and preterm labor, in contrast to those of cocaine. Experimental studies[98,143] demonstrated that cocaine stimulates myometrial contractility. It also causes constriction of the uterine arteries and reduces uterine blood flow, resulting in inadequate placental perfusion and fetal hypoxia[211]. Cocaine is transferred across the placenta and reaches the fetus causing sympathetic stimulation and fetal hypertension[211]. The vascular changes and increased uterine contractility induced by cocaine explain the acute obstetric pathology that may occur after cocaine use, such as abruptio placentae, a complication associated with preterm birth and stillbirth[2,55,129]. In opiate addicted women, factors associated with their addiction e.g drug withdrawal, infections [78,172,171] stressful life events[146] may be responsible for the

occurrence of preterm labor. In conclusion, the combination of opiates and cocaine in study group 3 may have caused the elevated incidence of preterm labor and delivery directly because of the pharmacologic properties of cocaine and indirectly through infections, stressful life events and other factors common to a population of drug addicts.

As in other studies[41,115,125], the incidence of cesarean section in drug dependent pregnant women was similar to that in controls. However, the indications for cesarean section in drug dependent women showed a prevalence of fetal distress as indicated by the fetal cardiotokogram. Most cases of cesarean section because of fetal distress occurred in women who abused both opiates and cocaine (group 3). No information about the reasons for cesarean section in drug dependent women could be found in the pertinent literature.

In agreement with previous reports[41,59,105,193] no difference was demonstrated between the condition of newborns of drug dependent women and controls as judged by the Apgar scores. Umbilical arterial acid-base values would have allowed a more sensitive assessment of neonatal condition than Apgar scores, but these values were not consistently available. Meconium stained amniotic fluid was observed slightly more often in the study groups, including the clean group, than in controls, but the difference was not statistically significant at the chosen threshold of $p < 0.01$. This observation should be interpreted with care because of the small numbers involved. According to the literature the incidence of meconium stained amniotic fluid is elevated in drug dependent pregnant women [59,156]. As an explanation it is postulated that the fetus of a woman addicted to opiates may undergo episodes of relative overdose and withdrawal; reduction of the opiate may increase the episodes of withdrawal[202]. In methadone users withdrawal may occur even if the daily dose is not changed during pregnancy, because the effective tissue concentrations of the drug decrease as a result of the changed metabolism of methadone in pregnancy[165].

Together with prematurity, low birthweight is an important source of morbidity and mortality in neonates of drug dependent mothers[7,54,55,86,88,108,154,156,158]. The results of the study show that women who completely terminated their drug use (group 1) delivered infants with birthweights equal to those in controls. Continuous opiate use in pregnancy, irrespective if it concerned methadone or heroin alone or in combination with cocaine and/or other drugs, appeared to result in small-for-gestational age newborns with proportionally reduced birthweight, length and head circumference. This effect was reduced but not neutralized by improved socioeconomic conditions, more psychosocial support or

antenatal care, as demonstrated by the results observed in the methadone-maintained women.

The impact of maternal drug abuse on fetal growth is complicated and may involve many different factors. Because all three drug dependent groups were similar with respect to age, gravidity, smoking habits and, with regard to groups I and II also in socioeconomic status and antenatal care, the association between reduced fetal growth and continued drug use during pregnancy cannot be explained by differences with regard to those variables. Of the obstetric complications known to affect fetal growth, infections were frequently recorded in the study population, in particular in the group that used both opiates and cocaine, but hypertensive disorders occurred with low and equal frequency in the study and control groups. The mechanisms by which social status exerts a biologic effect are less clear, although the relationship between socioeconomic disadvantage and low birth weight is well known. Socioeconomic disadvantage may indirectly influence birthweight by limiting access to good nutrition, accomodation and, in some countries, medical care, by producing stress, and by resulting in maladaptive behavior such as smoking, teenage pregnancy and substance abuse. In case of similar socioeconomic status and different race, a constant disadvantageous 5% racial gap was found for black low birthweight infants[83,108]. Because the socioeconomic status of the controls and the first two groups of drug dependent pregnant women were not very different from each other, race could have influenced birthweight only in the polydrug users group. However, because the majority of the study women were white, a racial influence on the mean birthweight in group 3 seems unlikely. Maternal prepregnancy weight and maternal weight gain during pregnancy also affect birthweight. The correlation between birthweight and maternal weight gain is statistically significant[134]. We were unable to assess this factor, because a correct estimate of weight gain during pregnancy requires knowledge of maternal weight before pregnancy or at least very early in gestation, an unknown variable in the majority of drug dependent women. On the other hand, maternal weight gain could only account for about 6% of the variance in birthweight[134]. Placental examination revealed a relatively small number of cases with infarction, which cannot account for the differences in birthweight between the study and control populations.

In conclusion, a significant impact on fetal growth of the factors discussed above seems unlikely, and the results of our study are suggestive of a direct pharmacologic effect of

opiates and/or cocaine on fetal growth. Experimental pharmacokinetic studies have demonstrated an irreversible reduction of 10-16% in the active uptake and transplacental transfer of amino-acids, caused by the effect of opiates and cocaine on placental cholinergic and opiate systems[176] and on placental amino-acid transporters in both the microvillous and basal membrane[49,50]. Although part of the fetal amino-acid deficit may be compensated by induction of new amino-acid transport systems[176], placental insufficiencies for amino-acid transport may explain, at least to some extent, the fetal growth retardation caused by nicotine, opiates and cocaine[49,50]. In case of cocaine use, part of the negative effects on fetal growth may be attributed to vasoconstriction, which may reduce uteroplacental blood flow and nutrient uptake. Also when cocaine passes across the placenta, fetal vaso-constriction follows and may result in vascular disruptions and infarctions in different organs, in particular bowel and brain[27,56,97]. In their review on cocaine exposure in pregnancy [164] Plessinger and Woods suggest that cocaine could also lead to a compensatory diminished fetal blood supply to nonvital organs, e.g the bowel, which could result in necrotizing enterocolitis in infants with intrauterine exposure to cocaine[56].

The present study was limited to the assessment of congenital defects diagnosed by ultrasound in the fetus, or shortly after birth. The study group contained six cases of fetal congenital malformations, compared with none in controls. A few uncontrolled heroin studies have reported an increased risk of fetal anomalies[89,160] but most studies on opiate addiction, generally also uncontrolled, have not shown an increase in birth defects[19,156, 174,192,213]. In contrast, the incidence of, in particular, urinary and cardiovascular malformations, has been shown to be elevated in pregnancies complicated by cocaine use[31,33,123,182,215]. Glantz and Woods[81] emphasize the importance of the experimental study reported by Webster and Brown-Woodman[81] on the effects of cocaine on rat embryos. Examination of the rat embryos 48 hours after maternal administration of cocaine revealed hemorrhages in the footplates, tail and genital tubercle, and the authors concluded that cocaine was responsible for hemorrhages and edema in already developed structures and that subsequent tissue necrosis resulted in limb reduction. Limb reduction was observed in one baby of the study group, whose mother had used large amounts of cocaine in the periconceptional period, and has also been reported in the literature[13,204]. A case was reported of an infant with, among other defects, a missing right ear, which could indicate that skin and cartilage tissues may also suffer from cocaine use[117]. Abnormal intracranial

structures have been detected in newborns exposed to cocaine in utero[52,133], most often areas of hemorrhagic infarction, probably due to episodes of vasospasm and hypertension induced by cocaine.

Signs of neonatal withdrawal from opiates are usually present shortly after birth, but may not reach a peak until 2-4 days of life or even as late as 2-3 weeks after birth[30,65,136]. About three-quarters of the number of babies in the polydrug group, but also more than half the number of infants born to mothers in the methadone group, had to be treated for signs of opiate withdrawal. The relationship between the maternal methadone dose and the severity of the neonatal withdrawal syndrome is still debated. Some studies found a significant association between the severity of withdrawal and the methadone dose during pregnancy[53,89,155], but other investigators[20,103,150] reported that the frequency and severity of signs of neonatal abstinence were not related to the maternal methadone dose. However, these studies did not have comparable doses of each drug, they did not consider the infant's maturity, and the numbers were small. Experimental pharmacodynamic and pharmacokinetic studies have demonstrated that, with continuous methadone exposure during pregnancy, gestational age-dependent changes occur in the maternal methadone plasma level and fetal metabolism [111,135,165,198]. These changes affect fetal drug exposure. Methadone also has a long half-life, which prolongs the duration of withdrawal in the neonate compared with that of heroin. Recently, the study of Doberczak et al[53] demonstrated a spectrum of relationships between maternal methadone dosage late in pregnancy, maternal methadone level, neonatal methadone level, rate of methadone decline in neonatal plasma and the severity of withdrawal signs related to the central nervous system. The general recommendation is to maintain an opiate addicted pregnant woman on the lowest effective dose of methadone since such a policy may have clinical benefits for the drug-exposed infant[30,53,155]. However, also a low dose methadone does not prevent a neonatal withdrawal syndrome and in our study group irregular, illicit drug use, in addition to a legally obtained but low dose of methadone, resulted in a high rate of withdrawal signs among the neonates born to polydrug dependent mothers. These results are in agreement with those obtained in earlier studies[69,89,153,155,159,185,192,213]. The greater opportunity to provide comprehensive antenatal care to the mother treated with a sufficient dose of methadone is associated with reduction or termination of illicit drug use, and with a decrease in the incidence of preterm delivery and low birthweight. Since the signs of withdrawal can be relatively easily

diagnosed and treated, the risk of occurrence of the withdrawal syndrome in infants exposed prenatally to methadone should be weighed against the risks of chronic use of an illicit opiate.

The neonatal mortality in the study group demonstrates two dangerous aspects of drug use in pregnancy: fetal death due to rapid detoxification and neonatal death due to early preterm birth after the use of large amounts of drugs. The question of whether or not to attempt complete detoxification during pregnancy is not easily answered. Detoxification is potentially dangerous because it may precipitate fetal distress[217] and may result in stillbirth[168]. On the other hand, as discussed earlier, opiates and cocaine have a dose-dependent deleterious effect on fetal growth and neonatal condition[41,53,89,155]. For that reason a policy of gradual detoxification was attempted in the pregnant drug dependent women of this study. The finding that the obstetric course and neonatal outcome of the detoxificated study patients of group 1 were similar to those of controls shows the benefits of such an approach. Of importance are also the psychosocial advantages of a drug-free mother who is able to take care of her children. Although complete detoxification of pregnant opiate dependent women from methadone is not generally recommended[111,165] and, if successful, is considered to last for only a short time[65,67] the results of our study support the view that each pregnant addict should be evaluated on an individual basis before choosing for methadone maintenance. Our study shows that in an integrated, comprehensive approach that includes health, psychosocial and addiction programs, complete termination of drug use in pregnancy may be obtained with good results for mother and child.

The study group recorded three cases of sudden infant death, a high incidence as compared with that in the general Dutch population, which varied between 1.16/1000 in 1983 and 0.41/1000 in 1992[48]; whether or not SIDS may result from antenatal exposure to drugs, in particular cocaine, remains a matter of controversy. The results of some studies indicate an elevated risk of SIDS in infants of substance-abusing mothers[32,45,58], whereas others found no difference with non-drug abusing controls[16]. Studies reporting SIDS in infants of substance abusing mothers often suffer from the same shortcomings: incomplete documentation about the mother's drug addiction, small sample sizes, selective reporting with the possibility that sudden infant death cases are over- or underreported, and many confounding variables such as smoking and alcohol[16]. The risk of sudden infant death syndrome may be slightly elevated after intrauterine exposure to drugs, but it seems

unlikely that it is as high as 150/1000 as initially reported by Chasnoff et al in 1989[26]. To establish a clear causal relationship between drug abuse in pregnancy and SIDS, large population studies are needed with adjustments for the many confounding variables.

Like other parents, also drug dependent parents experience feelings of loss and guilt after the death of their baby, irrespective of the cause, and they need support from those involved in their care. An example of successful support through the mourning process is given by one of the drug dependent mothers in this study; after her first pregnancy, characterized by severe drug addiction, ended preterm and was followed by the infant's demise, she faithfully and successfully followed the antenatal care program in her second pregnancy.

The expertise of Central Address in dealing with the problems of drug addicted mothers and their children grew during the years. The result was an intensification of the efforts to integrate psychosocial measures and medical treatment of drug dependent women. The results obtained in the period 1989-1992 show a higher proportion of positive final reports than in the preceding period, in agreement with the higher number of pregnant addicts who improved their drug behavior in pregnancy. The results of the integrated approach demonstrate that not only the course and outcome of pregnancy in drug dependent women can be improved, but that, when detoxification is carried out as part of a comprehensive program, the obstetric and neonatal results of drug dependent women may become equal to those in a drug-free population.

Although this study analyses the effects of drug dependence during pregnancy only, follow-up of the infants born to the study patients is needed to assess the morphologic effects described in this chapter on infant's future somatic, mental and social development.

Chapter 6

GENERAL CONSIDERATIONS AND CRITICAL POINTS OF THE ROTTERDAM INTEGRATED OBSTETRIC APPROACH

The Rotterdam model of comprehensive care of drug dependent pregnant women attempts to go beyond the bounds of obstetric care focussing on medical treatment to an expanded approach with equal and simultaneous care of drug dependence and psychosocial needs. Obstetric care is integrated in the care provided by professionals of other human service disciplines, such as social workers and substance abuse specialists. The results obtained with the integrated multidisciplinary approach in Rotterdam were presented and discussed in detail in Chapters 3,4 and 5, to answer the first and the second question of the audit formulated in the Introduction. In this chapter the positive aspects and the critical points of the Rotterdam multidisciplinary approach for drug dependent pregnant woman will be evaluated and recommendations will be presented to improve the design and implementation of the integrated obstetric approach, in an attempt to answer the third and last question of the thesis.

6.1 Positive aspects of the multidisciplinary approach to drug dependent pregnant women

1. The design of the protocol relies on the assumption that holistic care, provided in a sensitive, nonpunitive way will promote the drug dependent woman's compliance and will increase chances of an optimal outcome of pregnancy for mother and child. By addressing the multiple needs of a drug dependent obstetric patient, care providers participating in the program tried to convince the pregnant addict that others were really caring for her. By emphasizing the woman's own responsability, the program attempted to overcome the passivity, the low self-esteem and the sense of powerlessness that are characteristic in drug dependent individuals. The results

of the study show that this kind of "responsible support" strengthens the woman's commitment to change drug behavior and to participate in the antenatal program.

2. The protocol never surpassed the individual. Although the protocol was carried out in a standardized way, the holistic and psychosocial approach ensured that every woman received treatment and support as indicated by individual needs. The protocol guided the obstetric and psychosocial plan but did not dominate the relationship between the woman and the care provider.
3. The management was consistent, with clear directions for everyone involved in the program, including the drug dependent pregnant woman. Regular communication between the professionals involved in the program reduced the woman's tendency to manipulative behavior.
4. There was continuity in the obstetric care since it was performed by the same obstetrician, trained in problems of drug use in pregnancy, which stimulated the development of bonding between the pregnant addict and her obstetrician. All obstetric and neonatologic care providers (physicians, nurses) were fully informed about the approach to the care of drug dependent pregnant women.
5. The obstetric risks were mainly addressed through routine obstetric care; supplementary examinations were restricted to a minimum, and the time schedule of the antenatal visits was not altered.
6. Consistent application of the integrated obstetric approach resulted in the period 1989-1992 in an increased proportion of women who successfully reduced and stopped drug use during pregnancy, and in an improved outcome with regard to - fetal growth.
7. Treatment for drug addiction was provided by professionals in drug dependence simultaneous with the antenatal care. Detoxification and methadone maintenance were performed under supervision of an obstetrician and a physician trained in the management of drug addiction. The obstetric results showed a similar course and outcome of pregnancy in detoxificated women as in controls.
8. Informed consent had to be obtained before medical tests, including urinalysis, could be performed, and informed consent was also needed for the exchange of information between the professionals participating in the multidisciplinary program. It was emphasized that all information was confidential and provided only to those

concerned, and that the woman could always withdraw her consent. This stimulated the woman's compliance with the program.

9. The agreement to centralize the care for drug dependent pregnant women facilitated referral for antenatal and perinatal care, stimulated cooperation and communication between the participating institutions, and simplified the coordination work of Central Address. The expertise and efficiency of Central Address increased during the 10 years period of the study. The fact that in 1992 in Rotterdam 72% of children of drug dependent mothers were brought up by their parents in a safe environment demonstrates the success of the nonpunitive approach to the care of drug dependent mothers.

10. Medical, social, educational and child protective support were offered after delivery. Long-term pediatric follow-up, provided by pediatricians trained in the pediatric aspects of antenatal drug use, remains an important way of evaluating not only the long-term effects of fetal drug exposure but also those of a particular social environment on the development of a child.

6.2 Critical points of the multidisciplinary approach to drug dependent pregnant women

1. Although alcohol is considered to be abused more than drugs, alcohol use in pregnancy was not frequently identified.

2. Insufficient awareness of the cocaine problem most likely resulted in underestimation of the incidence of cocaine use among pregnant addicts in the period 1983-1988. This may have led to underreporting of obstetric complications related to cocaine use.

3. The pharmacologic treatment of opiate dependent pregnant women is open to criticism. From the results concerning methadone substitution it appears that the recommendation to maintain an opiate addict on the lowest effective dose of methadone was often interpreted as meaning that she should receive the lowest possible dose, which resulted in frequent illicit opiate use, with negative consequences for mother and child. This could have been avoided, at least in part, by the administration of a higher daily methadone dose.

4. A low incidence of Chlamydia infections was found, despite a high proportion of

sexually transmitted diseases and clinical urinary tract infections. Because drug dependent pregnant women were not screened for Chlamydia and a Chlamydia swab was not taken in cases with signs of urinary infection, it may be assumed that the study has underreported Chlamydia infections.

6.3 Recommendations for the integrated obstetric approach

Based on the critical points discussed above the following recommendations are presented and summarized in Fig. 6.1.

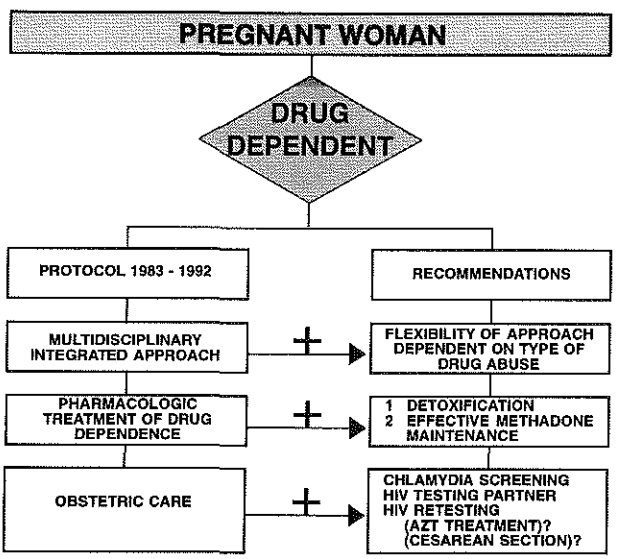


Fig. 6.1 Schematic presentation, including recommendations, of the integrated multidisciplinary approach for drug dependent pregnant women.

1. The program should aim at detoxification in motivated women whose socioeconomic conditions are stable and who participate in the comprehensive care provided during pregnancy. Rapid detoxification is contraindicated in pregnancy. Although the number of detoxificated women in this study is not large, it appears that coordinated, slow, detoxification results in a course and outcome of pregnancy similar to that in non-drug dependent controls and may last for a longer time than generally expected. This last observation is of great importance for a pregnant

addict since it may motivate her and all those taking care of her to reduce and stop drug use during pregnancy.

2. Methadone maintenance is preferable in all cases in which detoxification is not possible, because the obstetric results are good and preventive health and social plans may be expected to succeed in a stable, cooperative methadone user. In such cases, the disadvantages of methadone maintenance, such as fetal growth retardation and neonatal withdrawal syndrome, should be accepted. Because of changes in the methadone metabolism during pregnancy, determination of plasma methadone concentration may be helpful in achieving an adequate methadone dosis.

3. Chlamydia screening should be introduced in addition to the screening for other infections. All cases with signs and symptoms of urinary tract infection but sterile cultures should be screened for Chlamydia.

4. Adjustment of the obstetric protocol with regard to HIV infection should be taken into consideration in view of recent studies[10,42,62,113] suggesting that cesarean section[42,62] and in particular the ante-, intra- and postpartum treatment with zidovudine (AZT) may reduce the risk of vertical transmission to the fetus by 25.5% to 8.3%[42]. Pregnant women at risk should therefore be retested for HIV infection in the third trimester of pregnancy.
It is advised that it be tried to obtain information from the pregnant addict about her partner; if it appears that he is also using or has used intravenous drugs, an HIV test should be offered to him.

5. Follow-up of the infants born to drug dependent mothers is recommended in order to assess further physical and neurobehavioral development of these children.

6. The integrated obstetric approach may also be valid for other substance (e.g. alcohol) dependent pregnant women, but in such cases the principles of referral, tasks and cooperation between the institutions participating in the multidisciplinary approach should be redefined.

The ideal is that a drug dependent woman should have her addiction treated before becoming pregnant, but in the real world this goal is often not met. Nevertheless, the wish of any woman, also the drug dependent one, to give birth should be respected and supported. Beyond the protocol and the scientific criteria applied for an optimal obstetric care of drug dependent pregnant women remains one thought: the patient, in this case, the mother and her infant.

SUMMARY

This thesis concerns an audit study of the integrated multidisciplinary approach to obstetric care of drug dependent pregnant women in Rotterdam in the period 1983-92.

CHAPTER ONE is a general introduction. The reasons that led to the development and institution of an integrated multidisciplinary approach to the obstetric care of drug dependent pregnant women in Rotterdam are described. An audit study is proposed in order to assess the structure and execution of this approach and to evaluate the results obtained in a population of drug dependent women in the period 1983-92 as compared with the course and outcome of pregnancy in a control group of non-drug dependent pregnant women matched for age and parity; to analyze changes in pregnancy outcome in drug dependent pregnant women in the course of 10 years of consequent application of the multidisciplinary protocol; to detect the critical points of this approach and to outline measures to improve its design and implementation.

CHAPTER TWO deals with the design of the study. The selection criteria for the 187 drug dependent pregnant women and the equal number of non-drug dependent pregnant controls included in the study, the methods of data collection, the definitions of all variables used, and the methods of statistical analysis are described in detail. The standard protocol of antenatal and perinatal care, the expanded protocol applied to drug dependent pregnant women, and the Rotterdam integrated multidisciplinary approach are presented, together with the changes due to medical progress during the 10 years period of the study. A program of detoxification and methadone maintenance was carried out under supervision of physicians and obstetricians trained and experienced in the management of pregnant drug addicts. The integrated multidisciplinary approach to the obstetric care of drug dependent pregnant women is discussed in the light of the medical knowledge at the time of its introduction in Rotterdam in 1983.

CHAPTER THREE presents general characteristics of the drug and non-drug dependent pregnant women such as age, gravidity, parity, smoking and alcohol consumption.

Available data about the socioeconomic situation of the drug dependent women is added. The study group is divided into three categories, dependent on termination of all drug use in pregnancy (group 1, n=51), stabilization on methadone without illicit (poly)drug use (group 2, n=47) and continuation of illicit (poly)drug use, with or without the addition of legal methadone (group 3, n=89). Cocaine appeared to be used more frequently in the study period 1989-92 than between 1983 and 1988, which may be explained by an increasing awareness of the use of this drug as well as by a real increase in its use. The data reported in this chapter indicate that detoxification or stabilization on methadone may be successful and lasting, in particular in women who are nulliparous, have reasonable, stable socioeconomic conditions, and use the possibilities for comprehensive obstetric, drug and social care. Illicit drug use in addition to legally obtained methadone may to a certain extent be due to a lack of consistency in increasing the daily dose of methadone until opiate withdrawal symptoms and the search for drugs are suppressed.

CHAPTER FOUR describes the course of pregnancy from the first antenatal visit until delivery in drug dependent pregnant women and their controls. In the study groups 1 and 2 the participation in the antenatal care program was not significantly different from that in controls, but the polydrug group 3 enrolled significantly later in pregnancy and participated less regularly in the antenatal care program. Syphilis and hepatitis B infections were recognized with a high frequency among drug dependent pregnant women, in addition to other sexually transmitted diseases such as gonorrhea and trichomoniasis. The HIV seropositivity among drug dependent pregnant women was low (2%). The most frequent antepartum complications that necessitated hospitalization in drug dependent pregnant women were inadequate fetal growth (9%) and threatened preterm birth (13%), in particular in group 3. The occurrence of other complications of pregnancy in the study groups was not different from that in controls.

CHAPTER FIVE presents data about delivery, condition and size of the newborn. The likelihood of preterm delivery was significantly elevated in the polydrug using women of group 3 (odds ratio 6.6), but not in groups 1 and 2. The indication for cesarean section in the study groups was mainly fetal distress, but the incidence of 7.5% was equal to that in controls. The condition of the newborns as judged by their Apgar scores was similar in the

study groups and in controls. Birthweight, length and head circumference of the newborns of women of group 1, who became clean during pregnancy, were not different from controls, but the women of group 2 and in particular of the polydrug using women of group 3 showed a significantly increased incidence of small-for-gestational age infants. There is indirect evidence that this could be due to a direct pharmacologic effect of opiates or cocaine, or both, on fetal growth. Consistent application of the integrated obstetric approach was associated in the second period of the study (1989-92) with an increased proportion of women who terminated drug use and with a reduced incidence of fetal growth retardation. One case of fetal death and six cases of fetal anomaly were observed in drug dependent women in comparison with none in controls. The high incidence of 41% of psychosocial reports that were still undecided at the time of discharge of the mother in the first study period (1983-88) was reduced to 13% in the period 1989-92, in accordance with increasing efficacy of the integrated multidisciplinary approach.

CHAPTER SIX discusses the positive aspects and the critical points of the Rotterdam multidisciplinary approach to the obstetric care of drug dependent pregnant women, followed by recommendations meant to improve its design and implementation. The study shows that the best pregnancy outcome is obtained in detoxificated patients, but stabilization on methadone is also associated with an improved course and outcome of pregnancy. Stabilization of drug dependent pregnant women on an effective dose of methadone is recommended if detoxification cannot be achieved. Drug dependent pregnant women should be screened for Chlamydia infection. The protocol should reconsider the approach to HIV screening in view of recent studies about vertical transmission of the virus and possible treatment of the newborn; a second screening in the third trimester of pregnancy is recommended. The integrated multidisciplinary approach to the obstetric care of drug dependent pregnant women described in this thesis may also be applied to other substance (e.g. alcohol) dependent pregnant women.

SAMENVATTING

In dit proefschrift wordt een toetsend onderzoek beschreven van de geïntegreerde multidisciplinaire benadering van de verloskundige zorg voor drugs-verslaafde zwangeren in Rotterdam in de periode 1983-92.

HOOFDSTUK EEN geeft een algemene inleiding. De redenen die hebben geleid tot het ontwikkelen en instellen van een geïntegreerde multidisciplinaire benadering van de verloskundige zorg voor drugs-verslaafde zwangere vrouwen in Rotterdam worden beschreven. In een toetsend onderzoek zullen de opzet, de uitvoering en de resultaten worden geanalyseerd, die werden verkregen met deze benadering in de periode 1983-92, in vergelijking met die van een controlegroep van niet-drugsafhankelijke zwangeren, die overeenkomen voor wat betreft leeftijd en pariteit. Tevens zal worden nagegaan of in de periode van 10 jaar van consequente toepassing van het multidisciplinaire protocol veranderingen zijn opgetreden in de uitkomst van de zwangerschappen van drugs-verslaafde vrouwen. Tenslotte zullen punten van kritiek op deze benadering naar voren worden gebracht en zullen maatregelen worden beschreven om het protocol en de uitvoering ervan te verbeteren.

HOOFDSTUK TWEE behandelt de opzet van het onderzoek. De criteria worden besproken voor selectie van de 187 drugs-verslaafde zwangeren en een gelijk aantal niet-drugsverslaafde zwangere vrouwen, die als controle in het onderzoek werden opgenomen. De methoden van het verzamelen van de gegevens, de definities van de gebruikte variabelen en de methoden van statistische analyse van het materiaal worden gedetailleerd beschreven. Het standaard protocol voor antenatale en perinatale zorg en het uitgebreide protocol dat werd gehanteerd voor drugs-verslaafde zwangeren, worden besproken, in samenhang met het systeem van geïntegreerde multidisciplinaire benadering van de verloskundige zorg en de veranderingen die zich daarin gedurende de periode van 10 jaar van het onderzoek hebben voorgedaan. Een programma van detoxificatie en behandeling met methadon werd uitgevoerd onder toezicht van artsen en obstetrici met speciale kennis en ervaring in de begeleiding en behandeling van zwangere drugsverslaafden. De

geïntegreerde multidisciplinaire benadering van de verloskundige zorg voor drugs-verslaafde zwangeren wordt besproken tegen de achtergrond van de medische kennis betreffende dit onderwerp ten tijde van de invoering ervan in 1983.

HOOFDSTUK DRIE presenteert een aantal algemene kenmerken van de zwangeren in de studie- en de controlegroep, zoals leeftijd, graviditeit, pariteit, en leefgewoonten, zoals roken en alcoholgebruik. Ook worden beschikbare gegevens over de sociaal-economische achtergrond van de drugs-verslaafde zwangeren gepresenteerd. De onderzoeksgroep wordt in 3 categorieën verdeeld: zwangeren die het gebruik van drugs tijdens de zwangerschap geheel hebben gestaakt (groep 1, n=51); zwangeren die gestabiliseerd werden met behulp van methadon, zonder illegaal drugsgebruik (groep 2, n=47); en zwangeren die ook tijdens de zwangerschap hun patroon van illegaal gebruik van harddrugs onveranderd voortzetten, met of zonder toevoeging van legaal verkregen methadon (groep 3, n=89). In de onderzoeksperiode 1989-92 bleek cocaine door meer vrouwen te worden gebruikt dan in de periode van 1983-88. Dit kan wellicht worden verklaard door toegenomen bekendheid bij zorgverleners met cocaine, wellicht ook door een werkelijke toename van het gebruik. Uit de gegevens die naar voren worden gebracht in dit hoofdstuk, kan worden afgeleid dat detoxificatie of stabilisatie van zwangere drugsverslaafden met behulp van methadon met succes kan worden toegepast en dat het effect ervan blijvend kan zijn. Dit laatste geldt in het bijzonder voor nullipare vrouwen die leven onder redelijk stabiele sociaal-economische omstandigheden en die gebruik maken van de mogelijkheden voor geïntegreerde verloskundige en sociale zorg. Voortgezet illegaal gebruik van drugs onder legale behandeling met methadon kan, in ieder geval in een aantal gevallen, worden toegeschreven aan het in onvoldoende mate ophogen van de dagelijkse dosis methadon, zodat onthoudingsverschijnselen en het verlangen naar illegale drugs onvoldoende worden onderdrukt.

HOOFDSTUK VIER beschrijft het verloop van de zwangerschap, vanaf het eerste antenatale bezoek tot aan de bevalling, bij de in het onderzoek opgenomen drugs-verslaafde zwangeren en hun controles. In de onderzoeksgroepen 1 en 2 was de deelname aan de antenatale zorg niet verschillend van die bij niet-drugsverslaafde zwangeren. De zwangeren uit groep 3 begonnen echter significant later in de zwangerschap dan niet-verslaafde

controles met antenatale zorg en namen veel minder regelmatig daaraan deel. Lues en hepatitis B kwam frequent voor onder drugs-verslaafde zwangeren, evenals andere sexueel-overdraagbare ziekten zoals gonorrhoe en trichomoniasis. Het aantal HIV-seropositieve zwangeren in de onderzoeksgroep was laag (2%). De meest frequent voorkomende complicaties van de zwangerschap, die opname van drugs-verslaafde zwangeren nodig maakten, waren onvoldoende foetale groei (9%) en dreigende vroeggeboorte (13%), vooral in groep 3. Andere zwangerschapscomplicaties kwamen bij drugs-verslaafde zwangeren niet vaker voor dan in de controlegroep.

HOOFDSTUK VIJF beschrijft de bevalling in de onderzoeksgroepen en de controles, alsmede variabelen van de toestand, grootte en gewicht van de pasgeborenen. De kans op vroeggeboorte was significant verhoogd in groep 3 (odds ratio 6.6), maar niet in de onderzoeksgroepen 1 en 2. De belangrijkste indicatie voor sectio caesarea bij drugs-verslaafde zwangeren was foetale nood, maar de incidentie van sectio caesarea bij drugs-verslaafde zwangeren was met 7.5% gelijk aan die in de controlegroep. Er waren geen verschillen aantoonbaar tussen de onderzoeksgroepen en de controles voor wat betreft de toestand van de pasgeborenen, afgemeten aan de Apgar-score. Voor wat betreft het geboortegewicht, de lengte en de hoofdomtrek van de pasgeborenen waren er geen verschillen tussen onderzoeksgroep 1 en controles, maar in groep 2 en, vooral, in groep 3 was het voorkomen van kinderen met een te laag geboortegewicht significant verhoogd in vergelijking met de controlegroep. Dit zou kunnen worden veroorzaakt door een direct farmacologisch effect van opiaten of cocaine, of beiden, op de foetale groei. De consequente toepassing van de geïntegreerde multidisciplinaire benadering van de verloskundige zorg voor drugs-verslaafde zwangeren ging in de tweede onderzoeksperiode (1988-92) samen met een toeneming van het relatieve aantal zwangeren dat stopte met drugsgebruik tijdens de zwangerschap en eveneens met een verminderd voorkomen van foetale groeivertraging. In de groep drugs-verslaafde zwangeren kwam één geval voor van foetale sterfte en zes pasgeborenen met aangeboren afwijkingen. Foetale sterfte en aangeboren afwijkingen werden niet waargenomen in de controlegroep. Het grote aantal psychosociale adviezen in de eerste onderzoeksperiode dat ten tijde van het ontslag van de moeder nog niet was afgerond (41%) kon in de periode 1989-92 worden teruggebracht tot 13%, wat wijst op een toegenomen doeltreffendheid van het programma van geïntegreerde

multidisciplinaire benadering van drugs-verslaafde zwangeren.

HOOFDSTUK ZES beschrijft de positieve aspecten en de punten van kritiek van het Rotterdamse programma van geïntegreerde multidisciplinaire benadering van obstetrische zorg voor drugs-verslaafde zwangeren, gevolgd door aanbevelingen ter verbetering van de opzet en uitvoering van het programma. De resultaten van het onderzoek laten zien dat de beste uitkomst van de zwangerschap wordt verkregen bij zwangeren die het drugsgebruik geheel hebben gestaakt. Ook stabilisatie van het illegale drugsgebruik met behulp van een methadon-programma gaat echter samen met een significante verbetering van het verloop en de uitkomst van de zwangerschap. Als detoxificatie niet mogelijk is wordt daarom stabilisatie van drugs-verslaafde zwangeren aanbevolen met een dosis methadon die voldoende is om onthoudingsverschijnselen te onderdrukken. Drugs-verslaafde zwangeren dienen als routine te worden onderzocht op infecties met Chlamydia. In het licht van recente onderzoeken met betrekking tot de verticale transmissie van HIV en mogelijkheden, die zich beginnen af te tekenen, voor behandeling van de pasgeborene dient het protocol voor screening van drugs-verslaafde zwangeren, met een hoog risico op HIV-infectie, te worden herzien. Een tweede screening in het derde trimester van de zwangerschap wordt aanbevolen. De geïntegreerde multidisciplinaire benadering van de obstetrische zorg voor verslaafde zwangeren, die wordt beschreven in dit proefschrift, kan ook worden toegepast op zwangeren met andere vormen van verslaving, zoals alcohol.

REFERENCES

1. Abrams BF, Laros RK. Prepregnancy weight, weight gain, and birth weight. Am J Obstet Gynecol 1986; 154: 503-9.
2. Acker D, Sachs BP, Tracey KJ, Wise WE. Abruptio placentae associated with cocaine use. Am J Obstet Gynecol 1983; 146: 220-1.
3. Alary M, Joly JR, Moutquin JM, Labrecque M. Strategy for screening pregnant women for chlamydial infection in a low-prevalence area. Obstet Gynecol 1993; 82: 399-404.
4. Alger LS, Farley JJ, Robinson BA, Hines SE, Berchin JM, Johnson JP. Interactions of human immunodeficiency virus infection and pregnancy. Obstet Gynecol 1993; 82: 787-96.
5. Allen PM, Sandler M. Critical components of obstetric management of chemically dependent women. Clin Obstet Gynecol 1993; 36: 347-60.
6. Allen MH. Detoxification considerations in the medical management of substance abuse in pregnany. Bull NY Acad Med 1991; 67: 270-6.
7. Alroomi LG, Davidson J, Evans TJ, Howat R. Maternal narcotic abuse in the newborn. Arch Dis Child 1988; 63: 81-3.
8. Amaro H, Fried LE, Cabral H, Zuckerman B. Violence during pregnancy and substance use. Am J Public Health 1990; 80: 575-9.
9. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Third Edition, Washington DC, American Psychiatry Association, 1987.
10. Ammann AJ. Human immunodeficiency virus infection/ AIDS in children: the next decade. Pediatrics 1994; 94: 930-5.
11. Amon E. Premature labor. In: Medicine of the fetus & Mother, Ree EA, Hobbins JC, Mahonie MJ, Petrie RH (eds). JB Lippincott, Company 1992.
12. Anggard E, Gunne LM, Holmstrand J, McMahon RE, Sandberg CG, Sullivan HR. Disposition of methadone in methadone maintenance. Clin Pharmacol Ther 1974; 17: 258-66.
13. Anker van den JN, Cohen-Overbeek TE, Wladimiroff JW, Sauer PJJ. Prenatal diagnosis of limb-reduction defects due to maternal cocaine use. Lancet 1991; 338: 1332.

14. Anker van den JN, Mildner RJ, Sauer PJJ. Cocaïne en zwangerschap; wie betaalt de rekening? Ned T Geneesk 1993; 137: 118-31.
15. Baciewicz GJ. The process of addiction. Clin Obstet Gynecol 1993; 36: 223-31.
16. Bauchner H, Zuckerman B. Cocaine, sudden infant death syndrome, and home monitoring. J Pediat 1990; 117: 904-6.
17. Beasley RP, Hwang LY, Lin CC, Stevens CE, Wang KY, Sun TS, Hsieh FJ, Szmuness W. Hepatitis B immune globin (HBIG) efficacy in the interruption of perinatal transmission of hepatitis B virus carrier state. Lancet 1981; 388-93.
18. Bingol N, Fuchs M, Diaz V, Stone RK, Gromisch DS. Teratogenicity of cocaine in humans. J Pediat 1987; 110: 93-6.
19. Blinick G, Jerez E, Wallach RC. Methadone maintenance, pregnancy, and progeny. JAMA 1973; 225: 477-9.
20. Blinick G, Inturrisi CE, Jerez E, Wallach RC. Methadone assays in pregnant women and preogeny. Am J Obstet Gynecol 1975; 121: 617-21.
21. Blinick G, Wallach RC, Jerez E, Ackerman BD. Drug addiction in pregnancy and the neonate. Am J Obstet Gynecol 1976; 125: 135-42.
22. Broekhuizen FF, Utrie J, Van Mullem C. Drug use or inadequate prenatal care? Adverse pregnancy outcome in an urban setting. Am J Obstet Gynecol 1992; 166: 1747-56.
23. Burkett G, Yasin SY, Palow D, LaVoie L, Martinez M. Patterns of cocaine binging: Effect on pregnancy. Am J Obstet Gynecol 1994; 171: 372-9.
24. Calhoun BC, Watson PT. The cost of maternal cocaine abuse: I. Perinatal cost. Obstet Gynecol 1991; 78: 731-4.
25. Chasnoff IJ, Hatcher R, Burns WJ. Polydrug-and methadone-addicted newborns: a continuum of impairment ?. Pediatrics 1982; 70: 210-3.
26. Chasnoff IJ, Landress HJ, Barrett ME. The prevalence of illicit-drug or alcohol use during pregnancy and discrepancies in mandatory reporting in Pinellas County, Florida. N Engl J Med 1990; 322: 1202-6.
27. Chasnoff IJ, Bussey ME, Savich R, Stack CM. Clinical and laboratory observations. J Pediat 1986; 108: 456-9.
28. Chasnoff IJ, Griffith DR, MacGregor S, Dirkes K, Burns KA. Temporal patterns of cocaine use in pregnancy. Perinatal outcome. JAMA 1989; 261: 1741-4.

29. Chasnoff IJ. Methodological issues in studying cocaine use in pregnancy: a problem of definitions. NIDA Res Monograph 1991; 114; 55-65.

30. Chasnoff IJ. Drug and alcohol effects on pregnancy and the newborn. In: Miller NS. Comprehensive Handbook of Drug and Alcohol Addiction, M Dekker, 1991; chapter 7 131-45.

31. Chasnoff IJ, Burns WJ, Schnoll SH, Burns KA. Cocaine use in pregnancy. N Engl J Med 1985; 313: 666-9.

32. Chavez CJ, Ostrea EM, Stryker JC, Smialek Z. Sudden infant death syndrome among infants of drug-dependent mothers. J Pediat 1979; 95: 407-9.

33. Chávez GF, Mulinare J, Cordero JF. Maternal cocaine use during early pregnancy as a risk factor for congenital anomalies. JAMA 1989; 262: 795-8.

34. Chavkin W. Mandatory treatment for drug use during pregnancy. JAMA 1991; 266: 1556-61.

35. Cherubin CE, Millian SJ. Serologic investigations in narcotic addicts. I. Syphilis, lymphogranuloma venereum, herpes simplex, and Q fever. Ann Int Med 1968; 69: 739-42.

36. Cherubin CE. Infectious disease problems of narcotic addicts. Arch Intern Med 1971; 128: 309-13.

37. Chez RA. Discussion: methodological issues in assessment of pregnancy outcome. NIDA Res Monograph 1991; 114; 84-92.

38. Chirico G, Belloni C, Gasparoni A, Cerbo RM, Rondini G, Klersy C, Orsolini P, Filice G. Hepatitis B immunuzation in infants of hepatitis B surface antigen-negative mothers. Pediat 1993; 717-9.

39. Cohen SN, Neumann LL. Methadone maintenance during pregnancy. Am J Dis Child 1973; 126: 445-6.

40. Committee on infant and preschool child. The sudden infant death syndrome. Pediatrics 1972; 50: 964-5.

41. Connaughton JF, Reeser D, Schut J, Finnegan LP. Perinatal addiction: outcome and management. Am J Obstet Gynecol 1977; 129: 679-86.

42. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, VanDyke R, Bey M, Shearer W, Jacobson R, Jimenez E, O'Neill E, Bazin B, Delfraissy JF, Culname M, Coombs R, Elkins M, Moye J, Stratton P, Balsley J. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994; 331; 1173-80.

43. Crofford M, Smith AA. Growth retardation in young mice treated with dl-methadone. Science 1973; 181: 947-8.

44. Czeizel AE, Kodaj I, Lenz W. Smoking during pregnancy and congenital limb deficiency. Br Med J 1994; 308: 1473-6.

45. Davidson Ward SL, Bautista D, Chan L, Derry M, Lisbin A, Durfee MJ, Mills KSC, Keens TG. Sudden infant death syndrome in infants of substance-abusing mothers. J Pediat 1990; 117: 876-81.

46. Davidson Ward SL, Schuetz S, Krishna V, Bean X, Wingert W, Wachsman L, Keens T. Abnormal sleeping ventilatory pattern in infants of substance-abusing mothers. Am J Dis Child 1986; 140: 1015-20.

47. Day NL, Cottreau CM, Richardson GA. The epidemiology of alcohol, marijuana, and cocaine use among women of childbearing age and pregnant women. Clin Obstet Gynecol 1993; 36: 232-45.

48. de Jonge GA, Hoogenboezem J. Wiegedood in Nederland in de periode 1980-1993. Ned T Geneesk 1994; 138: 2133-41.

49. Dicke JM, Verges DK, Polakoski KL. Cocaine inhibits alanine uptake by human placental microvillous membrane vesicles. Am J Obstet Gynecol 1993; 169: 515-21.

50. Dicke JM, Verges DK, Polakoski KL. The effects of cocaine on neutral amino acid uptake by human placental basal membrane vesicles. Am J Obstet Gynecol 1994; 171: 485-91.

51. Dinsmoor MJ, Irons SJ, Christmas JT. Preterm rupture of the membranes associated with recent cocaine use. Am J Obstet Gynecol 1994; 171: 305-9.

52. Dixon SD, Bejar R. Brain lesions in cocaine and metamphetamine exposed neonates. Pediatr Res 1988; 23: 405A.

53. Doberczak TM, Kandall SR, Friedmann P. Relationships between maternal methadone dosage, maternal-neonatal methadone levels, and neonatal withdrawal. Obstet Gynecol 1993; 81: 936-40.

54. Doberczak TM, Thornton JC, Bernstein J, Kandall SR. Impact of maternal drug dependency on birth weight and head circumference of offspring. Am J Dis Child 1987; 141: 1163-7.

55. Dombrowski MP, Wolfe HM, Welch RA, Evans MI. Cocaine abuse is associated with abruptio placentae and decreased birth weight, but not shorter labor. Obstet Gynecol 1991; 77: 139-41.

56. Downing GJ, Horner SR, Likbridge HW. Characteristics of perinatal cocaine-exposed infants with necrotizing enterocolitis. Am J Dis Child 1991; 145: 26-7.

57. Dubowitz LMS, Dubowitz V, Goldberg C. Clinical assessment of gestational age in the newborn infant. J Pediat 1970; 77: 1-10.

58. Durand DJ, Espinoza AM, Nickerson BG. Association between prenatal cocaine exposure and sudden infant syndrome. J Pediat 1990; 117: 909-11.

59. Edelin KC, Gurganious L, Golar K, Oellerich D, Kyei-Aboagye K, Hamid MA. Methadone maintenance in pregnancy: consequences to care and outcome. Obstet Gynecol 1988; 71: 399-404.

60. Ellwood DA, Sutherland P, Kent Chester, O'Connor M. Maternal narcotic addiction: Pregnancy outcome in patients managed by a specialized drug-dependency antenatal clinic. Aust NZ J Obstet Gynaecol 19876; 27: 92-8.

61. Esteban JI, Esteban R, Viladomiu L, López-Talavera JC, González A, Hernández JM, Roget M, Vargas V, Genesca J, Buti M, Guardia J. Hepatitis B virus antibodies among risks groups in Spain. Lancet 1989; 294-6.

62. European Collaborative Study. Caesarean section and risk of vertical transmission of HIV-1 infection. Lancet 1994; 343: 1464-7.

63. European Collaborative Study. Risk factors for mother-to-child transmission of HIV-1. Lancet 1992; 339: 1007-12.

64. Feldman JG, Minkoff HL, McCalla S, Salwen M. A cohort study of the impact of perinatal drug use on prematurity in an inner-city population. Am J Public Health 1992; 82: 726-8.

65. Finnegan LP. Management of pregnant drug-dependent women. Ann NY Acad Sci 1978; 311: 135-46.

66. Finnegan LP. Treatment issues for opioid-dependent women during the perinatal period. J Psychoact Drugs 1991; 23: 191-201.

67. Finnegan LP, Hagan T, Kaltenbach KA. Scientific foundation of clinical practice: opiate use in pregnant women. Bull NY Acad Med 1991; 67: 223-39.

68. Finnegan LP, Reeser DS. The incidence of sudden death in infants born to women maintained on methadone. Ped Res (abs 248) 1978; 12: 405.

69. Finnegan LP. Effects of maternal opiate abuse on the newborn. Federation Proc 1985; 44: 2314-7.

70. Fitzhardinge PM, Steven EM. The small-for-date infant. II. Neurological intellectual sequelae. Pediatr 1972; 50: 50-7.

71. Frank DA, Zuckerman BS, Amaro H, Aboagye K, Bauchner H, Cabral H, Fried L, Hingson R, Kayne H, Levenson SM, Parker S, Reece H, Vinci R. Cocaine use during pregnancy: prevalence and correlates. Pediatrics 1988; 82: 888-95.

72. Fried PA. Prenatal exposure to tobacco and marijuana: effects during pregnancy, infancy, and early childhood. Clin Obstet Gynecol 1993; 36: 319-37.

73. Fulroth R, Philips B, Durand DJ. Perinatal outcome of infants exposed to cocaine and/or heroin in utero. Am J Dis Child 1989; 143: 905-10.

74. Gawin FH, Ellinwood EH. Cocaine and other stimulants. Actions, abuse and treatment. N Engl J Med 1988; 318: 1173-82.

75. George SK, Price J, Hauth JC, Barnette DM, Preston P. Drug abuse screening of childbearing-age women in Alabama public health clinics. Am J Obstet Gynecol 1991; 165: 924-7.

76. Germain M, Krohn MA, Hillier SL, Eschenbach DA. Genital flora in pregnancy and its association with intrauterine growth retardation. J Clin Microbiol 1994; 32: 2162-8.

77. Gerstein DR, Lewin LS. Treating drug problems. N Engl J Med 1990; 323: 844-8.

78. Gibbs RS, Romero R, Hilier SL, Eschenbach DA, Sweet RL. A review of premature birth and subclinical infection. Am J Obstet Gynecol 1992; 166: 1515-28.

79. Gilbert WM, Lafferty CM, Benirschke K, Resnik R. Lack of specific placental abnormality associated with cocaine use. Am J Obstet Gynecol 1990; 163: 998-9.

80. Gillogley KM, Evens AT, Hansen RL, Samuels SJ, Batra KK. The perinatal impact of cocaine, amphetamine, and opiate use detected by universal intrapartum screening. Am J Obstet Gynecol 1990; 163: 1535-42.

81. Glantz JC, Woods JR. Cocaine, heroin, and phencyclidine: obstetric perspectives. Clin Obstet Gynecol 1993; 36: 279-301.

82. Goodfriend MJ, Shey IA, Kein MD. The effects of maternal narcotic addiction on the newborn. Am J Obstet Gynecol 1956; 71: 29-36.

83. Gould JB, LeRoy S. Socioeconomic status and low birth weight: A racial comparison. Pediat 1988; 82: 896-904.

84. Green M, Silverman I, Suffet F, Taleporos E, Turkel WV. Outcome of pregnancy for addicts receiving comprehensive care. Am J Drug Alcohol Abuse 1979; 6: 413-29.

85. Gregler LL, Mark H. Medical complications of cocaine abuse. N Engl J Med 1986; 315: 1495-1500.

86. Hadeed AJ, Siegel SR. Maternal cocaine use during pregnancy: effect on the newborn infant. Pediatrics 1989; 84: 205-10.

87. Haglund B, Cnattingius S. Cigarette smoking as a risk factor for sudden infant death syndrome: A population-based study. Am J Public health 1990; 80: 29-32.

88. Handler A, Kistin N, Davis F, Ferré C. Cocaine use during pregnancy: Perinatal outcomes. A J Epidemiol 1991; 133: 818-25.

89. Harper RG, Solish GI, Purow HM, Sang E, Panepinto WC. The effect of a methadone treatment program upon pregnant heroin addicts and their newborn infants. Pediatrics 1974; 54: 300-5.

90. Harper RG, Solish G, Feingold E, Gersten-Woolf NB, Sokal MM. Maternal ingested methadone, body fluid methadone, and the neonatal withdrawal syndrome. Am J Obstet Gynecol 1977; 129:417-24.

91. Hart G. Syphilis tests in diagnostic and therapeutic decision making. Ann Int Med 1986; 104: 368-76.

92. Hawken J, Chard T, Costeloe K, Jeffries D, Grant K, Hudson C. Risk identification for HIV infection in an inner London antenatal population. Eur J Obstet Gynecol Reprod Biol 1994; 55: 141-4.

93. Hillis SD, Nakashima A, Marchbanks PA, Addiss DG, Davis JP. Risk factors for recurrent Chlamydia Trachomatis infections in women. Am J Obstet Gynecol 1994; 170: 801-6.

94. Hobel CJ, Ross MG, Bemis RL, Bragonier JR, Nessim S, Sandhu M, Bear MB, Mori B. The West Los Angeles preterm birth prevention project. I. Program impact on high-risk women. Am J Obstet Gynecol 1994; 170: 54-62.

95. Hoek van den JAR, Haastrecht van HJA, Goudsmit J, Wolf de F, Coutinho RA. Prevalence, incidence, and risk factors of hepatitis C virus infection among drug users in Amsterdam. J Infect Dis 1990; 162: 823-6.

96. Hogerzeil HV, Soepatmi S, Kreijenbroek M, Treffers PE. Aan heroine verslaafde zwangeren; een overzicht over 11 jaar uit het Wilhelmina Gasthuis te Amsterdam. Ned T Geneesk 1982; 126: 316-20.

97. Hoyme HE, Jones KL, Dixon SD, Jewett T, Hanson JW, Robinson LK, Msall ME, Allanson JE. Prenatal cocaine exposure and fetal vascular disruption. Pediatr 1990; 85: 743-7.

98. Hurd WW, Gauvin JM, Dombrowski MP, Hayashi RH. Cocaine selectively inhibits β-adrenergic receptor binding in pregnant human myometrium. Am J Obstet Gynecol 1993; 169: 644-9.

99. Hutchings DE, Hunt HF, Towey JP, Rosen TS, Gorinson HS. Methadone during pregnancy in the rat: dose level effects on maternal and perinatal mortality and growth in the offspring. J Pharmacol Exp Ther 1976; 197: 171-9.

100. Hutchings DE, Zmitrovich A, Brake SC, Malowany D, Church S, Nero TJ. Prenatal administration of methadone using the osmotic minipump: Effects on maternal and offspring toxicity, growth, and behaviour in the rat. Neurotoxic Teratology 1992; 14: 65-71.

101. James DK, Steer PJ, Weiner CP, Gonik B. High Risk Pregnancy Management Options, W.B.Saunders Company Ltd, London, England, 1994.

102. Kaltenbach K, Finnegan LP. Children exposed to methadone in utero. Ann NY Acad Sci 1989; 562: 360-1.

103. Kandall SR, Albin S, Gartner LM, Lee KS, Eidelman AI, Lowinson J. The narcotic-dependent mother: fetal and maternal consequences. Early Human Development 1977; 1/2: 159-69.

104. Kandall SR, Albin S, Lowinson J, Berle B, Eidelman AI, Gartner LM. Differential effects of maternal heroin and methadone use on birthweight. Pediatrics 1976; 58: 681-5.

105. Keith LG, MacGregor S, Friedell S, Rosner M, Chasnoff IJ, Sciarra JJ. Substance abuse in pregnant women: recent experience at the perinatal center for chemical dependence of Northwestern Memorial Hospital. Obstet Gynecol 1989; 73: 715-20.

106. Kimmel CA. Perspectives on the concern for and management of prenatal chemical exposure and postnatal effects. Ann NY Acad Sci 1989; 562: 1-2.

107. Klein RF, Friedman-Campbell M, Tocco RV. History taking and substance abuse counseling with the pregnant patient. Clin Obstet Gynecol 1993; 36: 338-46.

108. Kliegman RM, Rottman CJ, Behrman RE. Strategies for the prevention of low birth weight. Am J Obstet Gynecol 1990; 162: 1073-83.

109. Kliegman RM, Madura D, Kiwi R, Eisenberg I. Relation of maternal cocaine use to the risks of prematurity and low birth weight. J Pediatr 1994; 124: 751-6.

110. Kloosterman GJ. On the intrauterine growth. Int J Gynaecol Obstet 1970; 8: 895.

111. Kreek MJ. Methadone disposition during the perinatal period in humans. Pharmacol Biochem Behav 1979; 11: 7-13.

112. Krishna RB, Levitz M, Dancis J. Transfer of cocaine by the perfused human placenta: The effect of binding to serum proteins. Am J Obstet Gynecol 1993; 169: 1418-23.

113. Kuhn L, Stein ZA, Thomas PA, Sing T, Tsai W-Y. Maternal-infant HIV transmission and circumstances of delivery. Am J Publ Health 1994; 84: 1110-5.

114. Kuhnert BR. Drug exposure to the fetus - the effect of smoking. NIDA Res Monograph 1991; 114: 1-17.

115. Lam SK, To WK, Duthie SJ, Ma HK. Narcotic addiction in pregnancy with adverse maternal and perinatal outcome. Aust NZ J Obstet Gynaec 1992; 32: 216-21.

116. Lange de EE. De invloed van heroine en methadone op de zwangerschap en de pasgeborene. Ned T Geneesk 1979; 123: 1154-9.

117. Lessick M, Vasa R, Israel J. Severe manifestations of oculoauriculovertebral spectrum in a cocaine exposed infant. J Med Genet 1991; 28: 803-4.

118. Leveno KJ, Cunningham FG, Roark ML, Nelson SD, Williams ML. Prenatal care and the low birth weight infant. Obstet Gynecol 1985; 66: 599-605.

119. Lichtblau L, Sparber SB. Opiate withdrawal in utero increases neonatal morbidity in the rat. Science 1981; 212: 943-5.

120. Lifschitz MH, Wilson GS, O'Brian Smith E, Desmond MM. Fetal and postnatal growth of children born to narcotic-dependent women. J Pediat 1983; 102: 686-91.

121. Lin HH, Kao JH, Hsu HY, Ni YH, Yeh SH, Hwang LH, Chang MW, Hwang SC, Chen PJ, Chen DS. Possible role of high-titer maternal viremia in perinatal transmission of hepatitis C virus. J Infect Dis 1994; 169: 638-41.

122. Lindsay MK, Adefris W, Willis S, Klein L. The risk of sexually transmitted diseases in human immunodeficiency virus-infected parturients. Am J Obstet Gynecol 1993; 169: 103-5.

123. Little BB, Snell LM, Klein VR, Gilstrapp LC. Cocaine abuse during pregnancy: Maternal and fetal implications. Obstet Gynecol 1989; 73: 157.

124. Lundine S. Implications for New York state policy. Bull NY Acad Med 1991; 67: 315-9.

125. MacGregor SN, Keith LG, Chasnoff IJ, Rosner MA, Chisum GM, Shaw P, Minogue JP. Cocaine use during pregnancy: Adverse perinatal outcome. Am J Obstet Gynecol 1987; 157: 686-90.

126. Mahone PR, Scott K, Sleggs G, D'Antoni T, Woods JR. Cocaine and metabolites in amniotic fluid may prolong fetal drug exposure. Am J Obstet Gynecol 1994; 171: 465-9.

127. Maresh M. Audit in obstetrics and gynaecology. Blackwell Scientific Publications Inc. Cambridge, 1994.

128. Martin J, Payte JT, Zweben JE. Methadone maintenance treatment: A primer for physicians. J Psychoact Drugs 1991; 23: 165-76.

129. Mastrogiannis DS, Decavalas GO, Verma U, Tejani N. Perinatal outcome after recent cocaine usage. Obstet Gynecol 1990; 76: 8-11.

130. Matera C, Warren WB, Moomjy M, Fink DJ, Fox HE. Prevalence of use of cocaine and other substances in an obstetric population. Am J Obstet Gynecol 1990; 163: 797-801.

131. McCalla S, Minkoff HL, Feldman J, Glass L, Valencia G. Predictors of cocaine use in pregnancy. Obstet Gynecol 1992; 79: 641-4.

132. McFarlin BL, Bottoms SF, Dock BS, Isada NB. Epidemic syphilis: Maternal factors associated with congenital infection. Am J Obstet Gynecol 1994; 170: 535-40.

133. Mercado A, Johnson G, Calver D, Sokol RJ. Cocaine, pregnancy, and postpartum intracerebral hemorrhage. Obstet Gynecol 1989; 73: 467-8.

134. Metcoff J. Maternal nutrition and fetal development. Early Hum Develop 1980; 4: 99-120.

135. Mihaly GW, Morgan DJ. Placental drug trnasfer: effects of gestational age and species. Pharmac Ther 1984; 23: 253-66.

136. Miller WH, Hyatt MC. Perinatal substance abuse. Am J Drug Alcohol Abuse 1992; 18: 247-61.

137. Miller HC, Hassanein K, Hensleigh PA. Maternal factors in the incidences of low birthweight infants among black and white mothers. Pediat Res 1978; 12: 1016-9.

138. Miller NS. Nosology of drug and alcohol addiction. In: Comprehensive Handbook of Drug and Alcohol Addiction, M Dekker, 1991; chapter 14: 257-61.

139. Miller HC, Hassanein K, Chin TDY, Hensleigh P. Socioeconomic factors in relation to fetal growth in white infants. J Pediat 1976; 89: 638-43.

140. Minkoff HL, McCalla S,Delke I, Stevens R, Salwen M, Feldman J. The relationship of cocaine use to syphilis and human immunodeficiency virus infections among inner city parturient women. Am J Obstet Gynecol 1990; 163: 521-6.

141. Mittendorf R, Herschel M, Williams MA, Hibbars JU, Moawad AH, Lee K. Reducing the frequency of low birth weight in the United States. Obstet Gynecol 1994; 83: 1056-9.

142. Monga M, Weisbrodt NW, Andres RL, Sanborn BM. Cocaine acutely increases rat myometrial contractile activity by mechanisms other than potentiation of adrenergic pathways. Am J Obstet Gynecol 1993; 169: 1502-6.

143. Monga M, Weisbrodt NW, Andres RL, Sanborn BM. The acute effect of cocaine exposure on pregnant human myometrial contractile activity. Am J Obstet Gynecol 1993; 169: 782-5.

144. Moore TR, Sorg J, Miller L, Key TC, Resnik R. Hemodynamic effects of intravenous cocaine on the pregnant ewe and fetus. Am J Obstet Gynecol 1986; 155: 883-8.

145. Mulder-Kampinga GA, Boer K, Scherpbier HJ. HIV-infectie bij zwangere vrouwen in Nederland. Ned T Geneesk 1992; 136: 80-4.

146. Mutale T, Creed F, Maresh M, Hunt L. Life-events and low birthweight-analysis by infants preterm and small-for-gestational age. Br J Obstet Gynaecol 1991; 98: 166-72.

147. Naeye RL, Blanc W, Leblanc W, Khatamee A. Fetal complications of maternal heroin addiction: Abnormal growth, infections, and episodes of stress. J Pediat 1973; 83: 1055-60.

148. Neerhof MG, MacGregor SN, Retsky SS, Sullivan TP. Cocaine abuse during pregnancy: Peripartum prevalence and perinatal outcome. Am J Obstet Gynecol 1989; 161: 633-6.

149. Newman RG. Methadone treatment. Defining and evaluating success. N Engl J Med 1987; 317: 447-50.

150. Newman RG, Bashkow S, Calko D. Results of 313 consecutive live births of infants delivered to patients in the New York City methadone maintenance treatment program. Am J Obstet Gynecol 1975; 121: 233-7.

151. Ney JA, Dooley SL, Keith LG, Chasnoff IJ, Socol ML. The prevalence of substance abuse in patients with suspected preterm labor. Am J Obstet Gynecol 1990; 162: 1562-7.

152. Novati R, Thiers V, d'Arminio Monforte A, Maisonneuve P, Principi N, Conti M, Lazzarin A, Brechot C. Mother-to-child transmission of hepatitis C virus detected by nested polymerase chain reaction. J Infect Dis 1992; 165: 720-3.

153. Oats JN, Beischer NA, Breheny JE, Pepperell RJ. The outcome of pregnancies complicated by narcotic drug addiction. Aust NZ J Obstet Gynaec 1984; 24: 14-6.

154. Oro AS, Dixon SD. Perinatal cocaine and methamphetamine exposure: maternal and neonatal correlates. J Pediatr 1987; 111: 571-8.

155. Ostrea EM jr, Chavez CJ, Strauss ME. A study of factors that influence the severity of neonatal narcotic withdrawal. J Pediat 1976; 88: 642-5.

156. Ostrea EM jr, Chavez CJ. Perinatal problems (excluding neonatal withdrawal) in maternal drug addiction: a study of 830. J Pediat 1979; 94: 292-5.

157. Ostrea EM jr, Raymundo AL, Cohen F. The perinatal clinical profile of HIV infection in the pregnant addict. Ann NY Acad Sci 1989; 562: 375.

158. Ostrea EM jr, Raymundo AL. Has cocaine abuse increased perinatal morbidity in maternal drug addiction? Ann NY Acad Sci 1989; 562: 376.

159. Pelosi MA, Frattarola M, Apuzzio J, Langer A, Hung CT, Oleske JM, Bai J, Harrigan JT. Pregnancy complicated by heroin addiction. Obstet Gynecol 1975; 45: 512-5.

160. Perlmutter JF. Drug addiction in pregnant women. Am J Obstet Gynecol 1967; 99: 569-72.

161. Perlmutter JF. Heroin addiction and pregnancy. Obstet Gynecol Survey 1974; 29: 439-46.

162. Petitti DB, Coleman C. Cocaine and the risk of low birth weight. Am J Public health 1990; 80: 25-8.

163. Pierson PS, Howard P, Kleber HD. Sudden deaths in infants born to methadone-maintained addicts. JAMA 1972; 220: 1733-4.

164. Plessinger MA, Woods JR. Maternal, placental, and fetal pathophysiology of cocaine exposure during pregnancy. Clin Obstet Gynecol 1993; 36: 267-78.

165. Pond SM, Kreek MJ, Tong TG, Raghunath J, Benowitz NL. Altered methadone pharmacokinetics in methadone-maintained pregnant women. J Pharmacol Exper Ther 1985; 233: 1-6.

166. Racine A, Joyce T, Anderson R. The association between prenatal care and birth weight among women exposed to cocaine in New York City. JAMA 1993; 270: 1581-6.

167. Rajegowda BK, Glass L, Evans HE, Maso G, Swartz DP, Leblanc W. Methadone withdrawal in newborn infants. J Pediat 1972; 81: 532-4.

168. Rementeria JL, Nunag N. Narcotic withdrawal in pregnancy: stillbirth incidence with a case report. Am J Obstet Gynecol 1973; 116: 1152-6.

169. Richardson GA, Day NL, McGauhey PJ. The impact of prenatal marijuana and cocaine use on the infant and child. Clin Obstet Gynecol 1993; 36: 302-18.

170. Richardson GA, Day NL. Maternal and neonatal effects of moderate cocaine use during pregnancy. Neurotoxicol Teratology 1991; 13: 455-60.

171. Romero R, Avila C, Brekus CA, Morotti R. The role of systemic and intrauterine infection in preterm parturition. Ann NY Acad Sci 1991; 622: 355-75.

172. Romero R, Mazor M. Infection and preterm labor. Clin Obstet Gynecol 1988; 31: 553-84.

173. Rosen TS, Johnson HL. Children of methadone-maintained mothers: follow-up to 18 monthes of age. J Pediat 1982; 101: 192-6.

174. Rosner MA, Keith L, Chasnoff I. The Northwestern University drug dependence program: the impact of intensive prenatal care on labor and delivery outcomes. Am J Obstet Gynecol 1982; 144: 23-7.

175. Rusnak JM, Butzin C, McGlasson D, Blatt SP. False-positive rapid plasma reagin tests in human immunodeficiency virus infection and relationship to anti-cardiolipin antibody and serum immunoglobulin levels. J Infect Dis 1994; 169: 1356-9.

176. Sastry R. Placental toxicology: Tobacco smoke, abused drugs, multiple chemical interactions, and placental function. Reprod Fertil Dev 1991; 3: 355-72.

177. Schweitzer IL, Dunn AEG, Peters RL, Spears RL. Viral hepatitis B in neonates and infants. Am J Med 1973; 55: 762-71.

178. Shannon Burke M, Roth D. Anonymous cocaine screening in a private obstetric population. Obstet Gynecol 1993; 81: 354-6.

179. Shiraki K, Yoshihara N, Kawana T, Yasui H, Sakurai M. Hepatitis B surface antigen and chronic hepatitis in infants born to asymptomatic carrier mothers. Am J Dis Child 1977; 131: 644-7.

180. Silverman NS, Jenkin BK, Wu C, McGillen P, Knee G. Hepatitis C virus in pregnancy: Seroprevalence and ris factors for infection. Am J Obstet Gynecol 1993; 169: 583-7.

181. Slotkin TA. Perinatal exposure to methadone: how do early biochemical alterations cause neurofunctional disturbances? Progress in Brain Res 1988; 73: 265-79.

182. Slutsker L. Risks associated with cocaine use during pregnancy. Obstet Gynecol 1992; 79: 778-89.

183. Soepatmi S. De ontwikkeling van kinderen van drugafhankelijke moeders. Academic thesis, University of Amsterdam, 1992.

184. Soepatmi S. Kindergeneeskundige aspecten bij heroine- en methadongebruik in de zwangerschap. TGO 1986; 3: 269-75.

185. Soepatmi S. Pasgeborenen van aan heroine verslaafde moeders; een overzicht over 11 jaar uit het Wilhelmina Gasthuis te Amsterdam. Ned T Geneesk 1982; 126: 321-5.

186. Sowers JG. Preventive startegies in education: history, current practices, and future trends regarding substance abuse and pregnancy prevention. Bull NY Acad Med 1991; 67: 256-69.

187. Spence MR, Williams R, DiGregorio J, Kirby-McDonnell A, Polanski M. The relationship between recent cocaine use and pregnancy outcome. Obstet Gynecol 1991; 78: 326-9.

188. Sperling RS, Newton E, Gibbs RS. Intraamniotic infection in low-birth-weight infants. J Infect Dis 1988; 157: 113-7.

189. Spinillo A, Gorini G, Regazzetti A, De Seta F, Nicola S, Zara C. Asymptomatic genitourinary Chlamydia Trachomatis infection in women seropositive for human immunodeficiency virus infection. Obstet Gynecol 1994; 83: 1005-9.

190. Statzer DE, Wardell JN. Heroin addiction during pregnancy. Am J Obstet Gynecol 1972; 113: 273-8.

191. Stimmel B, Goldberg J, Cohen M, Rotkopf E. Detoxification from methadone maintenance: Risk factors associated with relapse to narcotic use. Ann NY Acad Sci 1978; 3: 173-80.

192. Stone ML, Salerno LJ, Green M, Zelson C. Narcotic addiction in pregnancy. Am J Obstet Gynecol 1971; 109: 716-23.

193. Strauss ME, Andresko M, Stryker JC, Wardell JN, Dunkel LD. Methadone maintenance during pregnancy: pregnancy, birth, and neonate characteristics. Am J Obstet Gynecol 1974; 120: 895-900.

194. Strauss ME, Ostrea EM, Stryker JC. Behavioral concomitants of prenatal addiction to narcotics. J Pediatr 1976; 89: 842-6.

195. Svigos JM, Robinson JS, Vigneswaran R. Threatened and actual preterm labour including mode of delivery. In: James DK, Steer PJ, Weiner CP, Gonik B. (eds). High Risk Pregnancy Management Options, W.B.Saunders Company Ltd, London, England, 1994.

196. Szeto HH, Umans JG, Umans HR, McFarland JW. The relationship between maternal and fetal plasma protein binding of methadone in the ewe during the third trimester. Life Sci 1982; 30: 1271-9.

197. Szeto HH. Discussion: Methodological issues in controlled studies on effects of prenatal drugs. NIDA Res Monograph 1991; 114: 37-44.

198. Szeto HH. Kinetics of drug transfer to the fetus. Clin Obstet Gynecol 1993; 36: 246-54.

199. Szeto HH. Maternal-fetal pharmacokinetics and fetal dose-response relationships. Ann NY Acad Sci 1989; 562: 42-55.

200. Thaler MM, Park CK, Landers DV, Wara DW, Houghton M, Veereman-Wauters G, Sweet RL, Han JH. Vertical transmission of hepatitis C virus. Lancet 1991; 338: 17-8.

201. Thomas DL, Cannon RO, Shapiro CN, Hook III EW, Alter MJ, Quinn TC. Hepatitis C, hepatitis B, and human immunodeficiency virus infection among non-intravenous drug-using patients attending clinics for sexually transmitted diseases. J Infect Dis 1994; 169: 990-5.

202. Umans JG, Szeto HH. Precipitated opiate abstinence in utero. Am J Obstet Gynecol 1985; 151: 414-4.

203. Vaughn AJ, Carzolo RP, Sanchez-Ramos L, Murphy S, Khan N, Chiu T. Community-wide estimation of illicit drug use in delivering women: Prevalence, demographics, and associated risk factors. Obstet Gynecol 1993; 82: 92-6.

204. Viscarello RR, Ferguson DD, Nores J, Hobbins JC. Limb-body wall complex associated with cocaine abuse: further evidence of cocaine's teratogenicity. Obstet Gynecol 1992; 80: 523-6.

205. Wadhwa PD, Sandman CA, Porto M, Dunkel-Schetter C, Garite TJ. The association between prenatal stress and infant birth weight and gestational age at birth: A prospective investigation. Am J Obstet Gynecol 1993; 169: 858-65.

206. Wallach RC, Jerez E, Blinick G. Pregnancy and menstrual function in narcotics addicts treated with methadone. The methadone maintenance treatment program. Am J Obstet Gynecol 1969; 105: 1226-9.

207. Watson RR. Drug abuse treatment. Drug and Alcohol Abuse Reviews 1992; 4: 1-10.

208. Webber MP, Lambert G, Bateman DA, Hauser WA. Maternal risk factors for congenital syphilis: A case-control study. Am J Epidemiol 1993; 137: 415-22.

209. Wilson GS, Desmond MM, Wait RB. Follow-up of methadone-treated and untreated narcotic-dependent women and their infants: health, developmental, and social implications. J Pediatr 1981; 98: 716-22.

210. Woods DL, Malan AP, Heese H. Patterns of retarded fetal growth. Early Hum Develop 1979; 3: 257-62.

211. Woods JR, Plessinger MA, Clark KE. Effect of cocaine on uterine blood flow and fetal oxygenation. JAMA 1987; 257: 957-61.

212. Zelson C, Lee SJ, Casalino M. Neonatal narcotic addiction. Comparative effects of maternal intake of heroin and methadone. N Engl J Med 1973; 289: 1216-20.

213. Zelson C, Rubio E, Wasserman E. Neonatal narcotic addiction: 10 year observation. Pediatrics 1971; 48: 178-89.

214. Zelson C. Infant of the addicted mother. N Engl J Med 1973; 288: 1393-5.

215. Zuckerman B, Frank DA, Hingson R, Amaro H, Levenson SM, Kayne H, Parker S, Vinci R, Aboagye K, Fried LE, Cabral H, Timperi R, Bauchner H. Effects of maternal marijuana and cocaine use on fetal growth. N Engl J Med 1989; 320: 762-8.

216. Zuckerman B. Selected methodologic issues in investigations of prenatal effects of cocaine: lessons from the past. NIDA Res Monograph 1991; 114: 45-54.

217. Zuspan FP, Gumpel JA, Mejia-Zelaya A, Madden J, Davis R. Fetal stress from methadone withdrawal. Am J Obstet Gynecol 1973; 122: 43-6.

ACKNOWLEDGEMENTS

I wish to express my gratitude to all those who have contributed to the realization of this thesis.

The study was made possible by the enthusiastic support of Prof.dr. H.C.S. Wallenburg, who gave me the opportunity to carry it out in the Institute of Obstetrics and Gynecology. His confidence, critical remarks, optimism and encouragement helped me through the sometimes difficult gestation of the study and the birth of the manuscript.

I acknowledge the dilligence of the members of the Thesis Committee, Prof.dr. W.J. Schudel, Prof.dr. I.D. de Beaufort, Prof.dr. H.K.A. Visser, in assessing the manuscript.

I want to thank all those who firmly believe in a multidisciplinary approach to the obstetric care of drug dependent women and who made the Rotterdam approach possible: the medical and non-medical staff of the Department of Obstetrics and of the Pediatric University Hospital Rotterdam, the Central Address, the Bouman Foundation, the Odyssee and the Bulldog Foundations, all drug institutions and clinics, therapeutic communities, GG & GD, Humanitas, the Child Welfare Council, nurseries and other institutions for youth care. My special thanks go to Gert Verwij and Bart Hendriks, together with their colleagues from Central Address, for the energy with which they coordinate the Rotterdam network for drug dependent pregnant women.

I am grateful to the obstetricians Fred Lotgering, Jim van Eyck and Tom Schneider and the pediatricians Professor P.J.J. Sauer and John van den Anker for the precise and complete documentation of their obstetric and pediatric care of drug dependent mothers and their infants. Many thanks to Jim van Eyck for putting me on the road of this study.

I am indebted to my colleagues on the 22nd floor of the Hoogbouw for their optimism and the moral support they gave me during the research period. I owe a special debt of gratitude to Piet Struijk who helped me with the statistical analysis of the data. Special thanks also to Jos van Blarkom, who prepared the manuscript under the stress of my deadlines. Cor van Dijk is responsible for drawing the figures and I thank him for his patience. Many thanks also to Wilma Spinnewijn, Wil Visser, Ilse Beckmann, Piet Struijk and Henk Bremer, who not only gave their invaluable help with the cutting and pasting of figures, but were also critical readers of the first drafts of the manuscript and, above all,

good friends.

I wish to thank my family and friends in and outside of Holland who stimulated and supported me all along.

Last but not least I wish to thank my parents, Gheorghe, Stefan and Carmen for their love, understanding and encouragement without which this thesis would never have been written.

CURRICULUM VITAE

	Born in Cluj, Romania
1974 - 1978	Gymnasium-β, Cluj, Romania
1978 - 1983	Medical School of the University of Cluj, Romania
1983 - 1984	Training in Internal Medicine at the University Institute Salvador Zubiran in Mexico City, Mexico
1985 - 1988	Medical School, EUR, Rotterdam, The Netherlands
1988 - 1989	Médecins sans Frontières, Brussels, Belgium
1989 - 1990	Department of Perinatal Medicine, University Hospital Rotterdam, The Netherlands
1990 - 1991	Dutch Institute for Alcohol and Drugs, Utrecht, The Netherlands
1991 - 1992	Resident, Department of Obstetrics and Gynecology, University Hospital Rotterdam-Dijkzigt, Rotterdam, The Netherlands
1992 - present	Research in Obstetrics, Institute of Obstetrics and Gynecology, EUR, Rotterdam, The Netherlands