Substitution therapy of infants for addiction and withdrawal. Possible links to sudden infant death (SID).

Literature review and case reports

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Abstract: Infants of mothers addicted to drugs are recognised to have a special risk for SID. The paper elucidates indications and clinical symptoms of different substitution therapies based on a literature review and clarified by case reports. For many infants the therapy has to be carried out during the whole first year of life or even longer. The case reports are focused on a family with drug addiction and affected by SID twice raising the question for respiratory depression due to high drug levels. Regarding this problem the records of a cardiac-respiration-monitor used for the infant who died second are introduced. The records had been made shortly before death and support our interpretation of morphological and toxicological findings.

Key Words: Drug addiction, methadone, withdrawal, treatment, SID, respiratory depression, monitoring.

Due to an increasing substitution frequency of drug addicts with methadone the number of parents among these patients has risen considerably. Approx. 36% of them have own children, highlighting the problems of drug taking during pregnancy. Maternal methadone dosages at delivery and severity of neonatal withdrawal have been shown closely related [1].

Commencing of the abstinence syndrome depends on the drugs used, dosage and time of last intake [2]. The syndrome may occur after an abrupt end of breast-feeding [3] or even delayed several weeks after finishing intake [4]. Neonatal withdrawal has been reported also for infants with maternal doses below 10 mg of methadone daily [5].

In the past recent years, attention given to the issue of methadone withdrawal during pregnancy has risen substantially [6].

Some consequences of drug taking during pregnancy had already been mentioned by Hippocrates who described intra-uterine suffocation of a foetus caused by intake of opium. Langstein [7] published about five children of women addicted to morphine. Three of them died soon after birth. Langlois et al. [8] reported on toxicological analyses in cases of suspected SID. Drugs were detected in 19 of 117 cases (16%) with a history consistent with SID, and in one of those cases death was attributed to methadone.

Its presence in two other cases was regarded as a possible contributing factor to death what had not been expected prior to examinations. Smialek et al. [9] found six cases positive for drugs among 130 cases of SID, one case of which involved methadone due to the mother’s treatment and in which methadone had apparently been transferred via breast-feeding.

Special problems may arise from the fact that cocaine is quite common in patients treated with methadone, and cocaine is believed to have reinforcing properties to an opiate-tolerant state.

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It has also been suggested that splitting the daily methadone dose into a twice-a-day regimen might lead to reduction of risks [10].

As withdrawal symptoms may be a frequent observation in infants born to mothers with drug abuse, Alroomi et al. [11] saw mild symptoms of drug withdrawal in 42% of infants born to women who continued taking heroin during pregnancy, but only nine of those newborns requiring treatment. SID occurred in two infants (four and six months old). Hoegermann et al. [12] found that among 9,000 infants per year born to narcotic-addicted women, 2-3% had been exposed to opiates in utero.

According to the Committee on Drugs of the American Academy of Pediatrics, neonatal abstinence syndrome may be severe, but cooperation to optimise the treatment of mothers and children is still lacking [13]. The average time interval to manifestation for early withdrawal ranged from approx. 24 to 72 hours post partum. Another interesting report from 1997 [14] suggests that there is no sufficient excretion of opiates by breast-feeding being in contrast to many other recent studies.

According to Blinick et al. [15], drug addiction in pregnancy can be managed two ways: detoxification and/or methadone-maintenance. Detoxification bears less complication for the child, but methadone-maintenance appears the most satisfactory approach with its complications being almost similar to those within the average obstetric population.

Contrary to this, in the 1970s diazepam was favoured for treatment of newborn’s withdrawal syndrome. An extensive study of Brown et al. [16] examined pregnant women receiving methadone-maintenance. Whereas head circumferences of their infants were significantly lower, there were no significant differences in birth weights. Other research revealed that 84.3% of women taking methadone were also positive for other drugs (cocaine 38%, opiates 41%, marijuana 44%) and that neonatal withdrawal was present in 72%.

However, birth outcome was not significantly different between methadone and cocaine users with mortality rates between 6.2 and 9.8 0/00 [17]. Other studies on methadone withdrawal during pregnancy indicate success with weaning programs without detrimental effects on foetuses and neonates [18].

Serious problems may arise from accidental methadone intoxications. Main causes appear to be prescription practice and distribution of methadone. It was found to be risky to issue combined prescriptions for e.g. seven days even for so-called reliable patients (behaviour without complaints for six months minimum). Furthermore, sometimes also improper containers were used and colour and sweet taste of the methadone solution are known to be attractive for children [19].

**Materials and methods**

Stress due to drug effects on of the newborn infant is described by ICD 779.5 as “neonatal withdrawal syndrome” being considered an independent disease since approx. 35 years [20]. In the Municipal Paediatric Hospital of Kassel (Germany) 57 newborn infants were treated within a three-year period in the 1990ies. A dramatic increase of infants requiring clinical concepts for care could be seen from this decade onwards. This study is focused on frequency and severity of pre- and postnatal morbidity, examining whether any impact from methadone programmes could be verified.

**Results**

**Statistical data on incidence and prevalence**

A rate of 57 neonates over 3 years 6 months means approx. 3% of all neonatological admissions to the hospital (n = 1,750) or 0.3% of all births in North Hesse (approx. 20,000) in this period. 40 of the 57 neonates showed withdrawal requiring therapy. Severity of withdrawal was classified according to the Finnegan Score [21, 22]. It was one or both of the parents of nearly 2/3 of the newborns (36 of 57) participating in a methadone programme. Approximately half of them showed urine tests positive for multiple drugs (20 of 36). Drug screening was negative in 12 of the 57 cases, although exposure could not be excluded by negative results of drug screening, as more than 50% of the infants showed withdrawal. 20% of the mothers showed combined drug-taking, as e.g. methadone and others with consumption of cocaine playing a secondary role only.

**Duration of withdrawal treatment**

The duration of administration of drugs given depends on the drugs detected. Withdrawal from methadone appeared to last considerably longer than that for heroin-taking. In case of combined drug-intake, the time-interval required for the administration of e.g. phenobarbitone was the same as for isolated methadone substitution. In newborns of cocaine-taking mothers, hospital stays were usually accompanied by withdrawal being particularly long and severe.

**Effects of methadone substitution on pre- and postnatal risks**

Participation in the methadone programme did not have apparent positive effects on duration of pregnancy or circumferences of the infants’ heads or body masses. Despite methadone substitution, general risks of drug-intake remained nearly unchanged as e.g. approx. doubling of early birth rates, hypotrophia and microcephalia.
There was also noted simultaneous abuse of nicotine exceeding 10 cigarettes daily by approx. 3/4 of the mothers.

The issue of postnatal mortality leads to medico-legal aspects. The mortality rate was very high, reaching extrapolated 9 to 10% as six of the 57 infants died (one child died outside the observation period). Two of the infants were very immature and born during acute withdrawal of their mothers (nos. 1 and 2). A third child died from pulmonary genital herpes infection acquired at birth. Symptoms of pneumonia developed from the fourth day, but diagnosis was made only post mortem. Three death cases (nos. 3 to 5) occurred within the context of SID following the neonatal period.

In all cases, monitoring had been performed, and the parents had also been trained in resuscitation: Infant no. 3 died two days after being discharged from hospital under unclear circumstances. The infants nos. 4 and 5 died 17 days following hospital treatment when they were not connected to the monitors. Infant no. 6 died with seven months during substitution with phenobarbitone, primarily revealing symptoms of SID, but medico-legal autopsy and toxicological analyses showed unexpected findings (see below).

### Table 1. Postnatal mortality (n = 57; 6 deaths)

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Birth in week of pregnancy</th>
<th>Body weight at birth (g)</th>
<th>Death on day of life</th>
<th>Circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>490</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Extreme immaturity</td>
</tr>
<tr>
<td>2</td>
<td>25&lt;sup&gt;th&lt;/sup&gt;</td>
<td>820</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>Immaturity; severe withdrawal</td>
</tr>
<tr>
<td>3</td>
<td>34&lt;sup&gt;th&lt;/sup&gt;</td>
<td>2.060</td>
<td>7&lt;sup&gt;th&lt;/sup&gt;</td>
<td>Herpes II – pneumonia</td>
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<tr>
<td>4</td>
<td>39&lt;sup&gt;th&lt;/sup&gt;</td>
<td>2.400</td>
<td>32&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>SID despite monitoring</td>
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<td>5</td>
<td>39&lt;sup&gt;th&lt;/sup&gt;</td>
<td>3.030</td>
<td>50&lt;sup&gt;th&lt;/sup&gt;</td>
<td>SID despite monitoring</td>
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<tr>
<td>6</td>
<td>37&lt;sup&gt;th&lt;/sup&gt;</td>
<td>2.480</td>
<td>7&lt;sup&gt;th&lt;/sup&gt; month</td>
<td>methadone +</td>
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### Case reports

**Infant no. 6 (tested positive for methadone/phenobarbitone/benzodiazepines)**

The almost hypotrophic but mature male neonate (37th week; Apgar score 7/9/10) showed discrete external findings (flattened dorsum of the nose, high forehead, hypertelorism, low ear nozzles).

The mother had been taking drugs for many years and received 15 ml of methadone daily.

Hospital admission was due to withdrawal and a suspected infection. From the 7th day, the infant was treated with phenobarbitone for increasing agitation with Finnegan scores decreasing from originally 14 below eight. Following temporary improvement, withdrawal and agitation deteriorated again two weeks later while the state of health was low suspected to be due to convulsions and severe respiratory infection.

However, the clinical conditions improved again, so that the infant was subsequently discharged from hospital with phenobarbitone-maintenance, after the parents had completed training for resuscitation and use of a monitor-unit. The course of the of the phenobarbitone levels was as follows (Finnegan scores < 8): initially 51.3 µg/ml, minimum of 22.3 µg/ml and prior to discharge 27.0 µg/ml.

During the following months, paediatric treatment was without major complications. Maintenance of phenobarbitone was continued according to hospital recommendations. Further periods of agitation occurred 3 to 4 weeks later, partly with considerable hyperexcitability, but contact to the paediatrician was only made for regular vaccinations and ongoing phenobarbitone prescriptions. Two weeks prior to death, the infant suffered from febrile bronchitis. An emergency physician prescribed amoxicillin and a mucolytic drug and phenobarbitone medication was continued with half of a 15 mg tablet three times daily.

The last six hours of the infant’s life showed several peculiarities: Following the last feeding at 7:45 pm (80 ml made from milk powder), the baby slept probably on its back, and distinct rhonchi were noted. At 11:30 pm, suddenly a loud wheezing was heard. The temperature had reached 40°C with the infant’s face “glowing”. Cold compresses helped to calm the baby down and it was laid next to her mother covered up to fall asleep again.

Around midnight the monitor-unit gave alarm due to tachycardia (figures 1 and 2). Another alarm was noted at 5:10 am, directly followed by resuscitation initially carried out by the parents and taken over by professionals (intubation and cardioversion). The baby was pronounced life extinct at 5:34 am.

The monitor-unit covered the two time-intervals from midnight to 0:11 am and 5:18 am until 5:35 am with stress especially prior to death. Tachycardia was rather monotone exceeding 220/min during the first period and accompanied by tachypnoea from 61 to 105/min. Contrary to this, a low heart rate was varying widely from 5:18 am with multiple intermittent periods of cardiac and respiratory arrests. Irreversible cardiac arrest occurred at 5:31 am and apnoea shortly later with changing respiratory rates during this period.

Forensic autopsy revealed a good state of nutrition, care, and general development. Internal findings were unremarkable except for pneumonia (focal and septal) accompanied by secondary reactions of other organs (myocarditis-like changes, septic spleen and mild...
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hepatitis). Microbiological samples from heart blood and middle ears were all sterile. However, Candida albicans and Klebsiella oxytoca were found in the tracheobronchial tree and Clostridium botulinum in intestinal contents.

Toxicology (FTIR) identified methadone in blood and GC/MS revealed 47 µg/ml methadone in gastric contents and 0.32 µg/ml in peripheral blood apart from 0.04 µg/ml EDDP and 15.0 µg/ml of phenobarbitone. According to SMIALEK et al. [9] the methadone levels were within the ranges for fatal intoxications in children. Additionally, a methadone level of 1,411 ng/ml and 431 g/ml of benzodiazepines were detected in urine. Methadone and benzodiazepines were outwith the prescribed medication and their sources remained unclear.

Infant no. 5

This baby had the same mother as no. 6 and was initially hospitalised for four weeks due to withdrawal. Another hospital stay became necessary because of excitation with screaming attacks and apnoeic phases. Several false monitor alarms were recorded but monitoring was continued. The last meal was given at 20:00 pm. The mother went to bed afterwards with her child lying next to the wall. When she woke up at 01:50 am the infant had foam around its mouth and looked “strangely”.

The monitor unit had raised no alarm, and only shortly later the baby was pronounced life extinct.

Forensic autopsy showed a body length of 51 cm with reduced dermal turgor and the anterior fontanelle distinctly sunken. The subcutaneous fatty tissue appeared pale (thickness only a few mm) and multiple subserous ecchymoses were noted (capsule of the thymus, pleura and lamina visceralis epicardi). Spotted lungs, focal pulmonary emphysema, haemorrhagic lung oedema and cerebral oedema were also present. Swelling of internal organs and liquid blood completed a pattern consistent with SID and negative toxicology results.

Discussion

SID in infants of narcotic-dependent mothers

Infants of drug-dependent mothers may have an increased risk of SID and show abnormalities of e. g. cardio-respiratory physiology. Monitoring is often used because of apnoeic episodes, not necessarily indicating that drug exposure itself causes SID [23]. Problems arising from drug abuse may include mild to severe developmental and cognitive problems depending on the substance used [24]. Older studies also revealed impairment of fetal growth for methadone taking mothers, but the main issue appears concomitant illicit drug use during pregnancy [25].

Fulroth et al. [26] reported on smaller average head circumferences for infants of heroin and cocaine abusers and Bauer [27] pointed out that this is due to combined effects of legal and illegal substances with a low socio-oeconomic status. Finnegan [28] also demonstrated links between drug-dependence, deficient pre/postnatal growth, vascular changes and hypoxic episodes resulting from a decreased oxygen carrying capacity.

Numerous studies have been published about a link between drug-addiction and SID. Rajegowda et al. [29] highlighted relevant autopsy findings in children younger than one year compatible with SID in approx. 2%. This rate was 5.5 times that of hospital populations.
Subsequent effects on respiratory control were thought to be responsible. Ward et al. [30] questioned in general whether substance abuse during the perinatal period represents a real risk factor for SID.

The SID rates of 0.88% among infants of substance abusing mothers compared to 0.12% among normal life births were not significantly different as well as ages at death (median of 63 vs. 91 days in drug-free infants), whereas symptomatic apnoea in infants of drug-abusing mothers showed a significantly higher incidence (22% vs. 5.4%).

Maternal substance abuse appears to have a high co-incidence with congenital malformations including cleft palate and gastrointestinal disorders. For a group of babies (n = 497) from mothers abusing a variety of drugs, Thomas [31] pointed out 10 times the normal rate for SID. Contrary to this, Ostrea et al. [32] stated that prenatal drug-exposure of infants, although associated with high perinatal morbidity, was not necessarily associated with an overall increase of mortality or incidence of SID during the first two years.

However, they observed a significantly higher mortality rate for low birth weight infants (≤ 2,500 g) positive for cocaine and opiates. Habel et al. [33] also reported a trend of association between maternal drug abuse and other factors contributing to an increased infant mortality for abusing mothers from 6.7 to 20.3 per 1,000 births. Drug-exposed infants were found to be more than three times likely to have low birth weights compared to the normal population.

Kandall and Kandall et al. [34, 35] found a SID rate in drug-exposed infants of 5.83 per 1,000 compared to 1.39 in infants without drug exposure. Higher frequencies were noted in infants exposed to opiates alone versus cocaine-exposed babies varying from 4.09 to 12.28 compared to 1.0 to 1.7 (for all drugs), with seasonal variations but ages not differing. Lutiger et al. [36] also saw a link between cocaine use and pregnancy outcome with a meta-analysis of 45 scientific papers revealing a higher risk for death in utero apart from genito-urinary tract malformation. Other authors also found highly significant effects of cocaine exposure. Cocaine is also thought to heart rate variability [37]. Mehta et al. [38] also reported on 68 infants with intra-uterine cocaine exposure with a significant decrease of heart rate variability.

**One current clinical concept for care (The Kassel concept)**

There are three different phases, namely before, during, and following birth. The pre-natal phase has to commence as early as possible. The Kassel concept for treatment of drug-withdrawal includes supervision of substitution, early detection of risks and offers of help already during pregnancy. It also intends dosage reduction under gynaecologic control. Main partners are gynaecologists, methadone ambulances and centres for perinatal medicine. Early contacts with centres for perinatal medicine appear to be of eminent practical and prognostic value.

The following (perinatal) period focuses on diagnosis and therapy of withdrawal according to the Finnegan Score aiming at therapy by e.g. early phenobarbitone substitution [39] by the use of which the duration of symptoms can be significantly shortened compared to morphine-hydrochloride (12.8 vs. 17.6 days) [4]. Rohrmeister et al. [40] also found that duration of withdrawal after buprenorphine exposure was significantly shorter compared to methadone and morphine. Approx. 70% of the newborns in our study showed withdrawal symptoms requiring treatment with phenobarbitone.

Simultaneous monitoring was performed as well as instruction of the parents including resuscitation training.

Within a few weeks, the third (postnatal) phase commences, now focused on reduction of phenobarbitone maintenance. Support and a close-meshed control of the social situation were indispensable as well. Contrary to phase one and two, the main tasks were now up to resident paediatricians and social medical services.

**Controversial discussion about different drugs used for withdrawal treatment**

The literature shows a controversial discussion about different drugs to treat withdrawal in neonates. Bläser et al. [41] found severe symptoms associated with methadone whereas buprenorphine appears less symptomatic. Their first choice for treatment was phenobarbitone with morphine preparations as second choice only. Previous intake of methadone resulted in protracted hospital stays especially with methadone dosages above 20 mg/d. In a study from Israel around 96% of newborns from drug addicted mothers developed Finnegan scores above 8 [42].

The authors favoured a combined tincture of opium and/or phenobarbitone. A review from Ireland found the same procedures for treatment with the duration of withdrawal being only loosely linked to the drug type and recommended morphine sulphate only to treat pure opiate withdrawal [43].

Research from Scotland [Glasgow; 44] found 53 of 64 infants suffering from withdrawal and most of them showing symptoms within 72 h post partum. Infants exposed to methadone had symptoms for longer, but required less treatment than those exposed to heroin with phenobarbitone being the preferred medication. Besides, methadone maintained mothers appear to come from more stable socio-economic conditions and care significantly better for their babies [45].
Dashe et al. [46] examined whether maternal methadone dosage affects duration and degree of neonatal withdrawal and saw dosages correlating closely with abstinence scores and durations of hospitalisation. Kuschel et al. [47] recommended cord and serum methadone levels useful in predicting severity of withdrawal. Infants needing treatment showed significantly lower methadone levels in cord blood than those not requiring. Lainwala et al. [48] examined lengths of hospital stays with methadone vs. oral morphine preparations and found no significant difference.

Ebner et al. [49] found the mean duration from birth to withdrawal requiring treatment was 33 h for morphine, 34 h for buprenorphine and 58 h for methadone. A meta-analysis by Osborn et al. [50] points into the same direction with opiates vs. phenobarbitone showing no significant difference in failure. While opiate treatment may be restricted to infants of mothers using opiates it appears to reduce the time to regain birth weight [51]. Lejeune et al. [52] investigated 246 cases with methadone or buprenorphine treatment with the effects being similar for methadone and high dose buprenorphine.

Kayemba-Kay’s et al. [53] examined 13 infants developing buprenorphine-related withdrawal requiring treatment but with buprenorphine appearing safe during pregnancy. Blandthorn et al. [54] support this view as around 24% of infants from mothers receiving methadone or buprenorphine required medication for withdrawal.

Chlorpromazine and combinations of clonidine and chloral hydrate are also used to treat withdrawal in neonates. However, based on a meta-analysis, Osborn et al. [55] found only insufficient evidence to support the use of chlorpromazine or clonidine in neonates. Mazurier et al. [56] compared durations of treatment with chlorpromazine vs. morphine hydrochloride with maternal characteristics (duration/type of addiction). Mean duration of treatment with chlorpromazine were significantly shorter compared to morphine hydrochloride but hospitalisation days were similar [57].

**Relevant patho-physiological effects of drug-exposure on the neonate**

Silvestri et al. [58] examined 114 neonates by pneumocardiograms for the effects of cocaine on respiratory and heart rates. Neonates exposed to cocaine without opiates showed the longest durations of apnoeas, more bradycardiac episodes, decreased periodic respiration and lower average heart rates than controls. Combinations of cocaine and opiates often resulted in periodic breathing.

Chasnoff et al. [59] found a rate of SID in infants prenatally exposed to cocaine around 15% vs. only 4% in infants exposed to opiates making cocaine more likely to result in cardio-respiratory abnormalities, possibly due to a decreased response to carbon dioxide. Experiments on mild hypoxia and hypercapnia revealed reactions significantly less intense in infants of drug addicted mothers with periodic breathing four times more likely than in children with heart rates significantly higher before, during and following hypoxic strains [60, 61]. Olsen et al. [62] demonstrated a significantly decreased sensitivity to carbon dioxide in infants exposed to methadone persisting for 15 days average. However, the time required to achieve a normal slope was not found related to maternal methadone dosage, neonatal serum methadone levels, severity of and therapy for methadone withdrawal [63].

**Postnatal morbidity**

Opinions on the effects methadone maintenance differ widely. Older studies found improvement of fetal growth and perinatal outcome [64]. Functional disturbances and infectious diseases were the main issues, possibly due to an increase of the metabolic rate during withdrawal [65]. Prone position and bed sharing may cause additional effects [66]. Infectious diseases were only secondary in the 57 newborns of our study as there was no case of hepatitis C or HIV-positivity. This lack of infections may be caused by the drug-scene in North Hesse developing rather late. Another reason may be higher general awareness in pregnant women. Furthermore, 2/3 of the 57 newborn infants showed maternal antibodies against hepatitis B and hepatitis C. Bacterial infections, cytomegaly and herpes had only five manifestations, with pneumonia of herpes type II causing death in one neonate.

**The infant positive for methadone (case no. 6)**

This baby showed therapeutic blood/serum levels of methadone and of course phenobarbitone at death, although the paediatrician had not issued a prescription for methadone. Focal and septal pneumonia were present, together with inflammatory changes of internal organs (myocarditis, chronic hepatitis, glomerulonephritis and non-acute meningitis) representing considerable stress factors as monitored cardiac and respiratory rates within the last hours prior to death were extremely changing immediately prior to death.

So this case was characterised by a number of adverse effects. All factors apparently lead to acute decompensation, which could be described as SID in its wider sense. But in our opinion one cannot seriously talk about SID according to its generally accepted definition. Investigations by the procurator fiscal were finally dropped although there was never provided an explanation for the presence of methadone in the baby.
Final conclusions

Over the past recent years, the number of methadone maintained patients in Germany has markedly risen. There is an indication that methadone dosage and severity of neonatal delivery are linked together. Not all of the newborns require treatment but there are detoxification and substance substitution as main alternatives.

In this study 40 out of 57 neonates required treatment for withdrawal, mostly caused by maternal intake of methadone but also other drugs. Methadone maintenance did not appear to have positive effects on pregnancies and neonates. Six of the 57 infants died and one of them was tested positive for methadone and benzodiazepines in addition to a prescribed phenobarbton medication. The last period of life of this baby was demonstrated using original monitor records revealing considerable stress.

Developmental alterations due to drug exposure include e.g. cognitive problems, impairment of fetal growth, smaller average head circumferences, vascular changes, congenital malformations, reduced birth weights, and serious disabilities or gastro-intestinal disorders. Clinical concepts for care have difficult aims during the three periods preceding, around and following birth. Early contacts with appropriate centres are essential with the Kassel concept favouring substitution of neonates with phenobarbton.

Effects of such drug exposure of newborns are e.g. longer durations of apnoea, decreased periodic respiration and lowered average heart rates with cocaine appearing one main factor. There may also be a decreased ventilatory response to elevated carbon dioxide levels, abnormal sleeping ventilatory patterns and longer sleeping times highlighting impaired repertoires of protective responses to hypoxia and hypercapnia. Additional effects may result from a prone sleeping position and co-sleeping with impacts especially on temperature regulation.

The controversial discussion about the usefulness of different drugs for treatment of withdrawal in neonates include recommendations for buprenorphine, tincture of opium, phenobarbton, benzodiazepines, morphine hydrochloride, chloral hydrate, chlorpromazine and clonidine. Phenobarbton appears to allow the shortest treatments with lesser side-effects but recommendations for drugs depend widely on individual research groups.

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