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Methadone treatment for pregnant heroin addicted women

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Summary

A review of methadone-related issues and the approach to heroin addicted patients is presented with the aim to clarify what is practiced by the establishment of anti-craving treatment and what is expected within a history of addiction. A series of clinical situations occurring throughout pregnancy to early child development are described, and the etiological hypothesis discussed. Moreover, some methodological considerations are described in order to better understand some ambiguity about the effectiveness and harmlessness of methadone treatment, particularly with regard to neonatal opiate withdrawal. Limitations to the outcome of pregnancies in heroin addicted women seems to be due to misconceptions about methadone toxicity and neonatal damage, which may lead to the mishandling of methadone as a therapeutic modality, especially with regard to maintenance at effective dosages.

Key Words: Pregnancy; Heroin Addiction; Methadone Treatment; Neonatal Withdrawal Syndrome

1. Methodological and conceptual issues

In some cases, treatment of pregnant addicted women is flawed by major omissions and misconceptions. For example, methadone treatment is often regarded as substitution, pointing at its withdrawal-preventing usefulness, which has little to do with its actual employment in an anti-craving and behaviour-modifying view. The main goal of treating women with methadone should be that of minimizing illicit opiate use throughout pregnancy, and to permit them to normalize their health and psychosocial issues. Effective dosages are associated with better outcome. Opiate abusing pregnant women, who are currently receiving methadone treatment, should have their dose increased to control craving. The use of ineffective dosages will produce an incomplete opiate blockade and can be harmful to the pregnancy, causing an unstable intrauterine environment and potentially foetal withdrawal. Apart from a minority of addicted patients who are able to stop using heroin at low doses, the majority re-

ceiving less than 80 mg/day will continue abusing practices combining substances in a struggle against the blockade. In such settings, these low dose treated patients may have a worse outcome than untreated addicts. Since most authors agree on the global benefit of effective methadone doses on the course of pregnancy in opiate-addicted mothers, when evaluating treatment effectiveness, in addition to receiving adequate doses, they should be provided with comprehensive services within structured programs especially designed to meet their needs.

2. Premises

Heroin addiction during pregnancy is associated with increased rates of perinatal morbidity, including spontaneous abortion, premature delivery, meconium stained liquor, neonatal infection and withdrawal syndromes varying according to which substance has been abused [18, 53]. Recurrent exposure to fast-acting, short-lasting opiates produces

a condition of continuous swinging from states of opiate intoxication and withdrawal due to a heightened tolerance level to their narcotic action. Fluctuations of opioid concentrations result in an irregular blood supply to the utero-placental unit and the foetus suffers from recurrent hypoxia. Such a mechanism is responsible for delayed foetal development, foetal death and morbidity [18]. Providing opiates equivalent in potency, but characterized by long-lasting, slow-acting kinetics and administered in a maintenance schedule, will normalize opioid metabolism of tolerant individuals and prevent foetal damage.

As for addiction-related issues, a series of additive behaviours may imperil pregnancy: lack of use of sterile equipment, sexual promiscuity, the involvement in violent acts, decreased hygiene, environmental influences, poverty, and refusal to comply with the health supporting guidelines of treatment facilities. The main goal of effective addiction treatment is that of leading addictive behaviour to extinction and normalizing opioid metabolism. Beyond tolerance/withdrawal related issues, the clinical correlates of opioid metabolism are of a behavioural nature, so that increasing dosages of therapeutic opiates can override the compulsion to seek illicit opiates.

Some opiates, such as methadone, display pharmacological characteristics which allow a health-promoting interaction with the brain due to the possibility of behavioural control and long-term damage reversal, at least in less severe cases. Methadone maintenance has been the standard treatment, and the only treatment approved for pregnant heroin addicts [12, 34]. As for non-pregnant addicted individuals, adequate methadone dosing is crucial to enhance compliance to treatment guidelines and achieve health objectives [13]. Even at no blocking dosages, pregnant heroin addicts' behaviour is modified enough to allow attendance at healthcare facilities and to obtain abstinence from cocaine by voucher incentives [19, 32-34, 67]. Methadone treatment may render women capable of attending services without any short-term or monetary advantage [67]. Given the combined benefit for both the mother and the foetus, and the potential double damage caused by treatment omission or delay, pregnant addicts, who apply for treatment, should be given priority for enrolment in methadone maintenance programs.

3. Teratogenicity and pregnancy abnormalities

No congenital abnormalities have been related to methadone. The widespread exposure of opioid abusing mothers to methadone in therapeutic settings provides an opportunity to normalize the pregnancy and prevent untoward damage to the foetus. When evaluations of drug-induced abnormalities are performed on neonates of women undergoing treatment, the role of poly-drug abuse and alcohol abuse should be considered [1]. Methadone exposed newborns have been reported to have higher birth weights and less morbidity

than heroin exposed babies. A trend towards increased birth weight has been reported by Hagopian et al., 1996 [24]. No delivery abnormalities have been noted in women who have followed successful methadone maintenance during their pregnancy.

4. Methadone management during pregnancy

Methadone metabolism in pregnancy is different than that of the non-pregnant patient and is influenced by the increased body fluid of pregnant women, especially during the 3rd trimester [68]. Methadone elimination is more rapid in pregnant women, so that the half-life is significantly shorter and methadone absorption may be also reduced [13, 30]. In blood sampled from the same subjects, peak methadone levels after equal oral dose loads are lower in the pre- than in the post-partum phase [43]. When withdrawal symptoms are monitored in a population of heroin abusing pregnant women entering methadone treatment at variable stages of their pregnancy, symptomatic women display methadone serum levels below the 0.211 mg/l [27], while administered dosages are similar. [Also a discrepancy seems to occur between higher methadone dosages and foetal serum levels of the drug: this latter tend to be similar regardless of increases of oral maternal dosages [14]. It should be remembered that different oral dosages may actually correspond to similar blood levels: therefore, such discrepancy may have no actual implication as long as the administration of methadone to pregnant women is rather based on clinical needs than on a scale of absolute oral dosage value [15]. As a consequence, some pregnant heroin addicts are provided ineffective medication due to unjustified cautions by the clinician [20].

5. Neonatal abstinence syndrome in methadone-exposed newborns

Since opiates traverse the placental barrier and foetal tissues become tolerant to their presence, the sudden deprivation of an opioid source at delivery may result in a withdrawal state, called the neonatal abstinence syndrome (NAS). More than one substance may be involved, and one should be aware of the possibility of a combined tolerance to opiates and gabaergic neurodepressants (benzodiazepines). NAS occurrence is variable and is generally seen in 60 to 90% of exposed neonates [6, 16, 26, 54, 59].

NAS intensity is widely variable. Onset of abstinence seems to depend on the interaction between the newborn's slow metabolism and the agents' own slow dissociation from binding sites. Long acting morphine substitution is not preferable to methadone in preventing the occurrence or severity of neonatal withdrawal [21]. When buprenorphine was evaluated, withdrawal was rated as milder and hospitalization time was consistently shorter [56].

Symptoms generally occur within 72 hours. The course

of withdrawal traverses a period of a week to several weeks with a gradual decrease in intensity within an undulating pattern. During this period the infant can gradually be stabilized [70]. Duration of hospitalization is generally longer for methadone than for heroin withdrawal. Polydrug abuse further contributes to the duration of withdrawal symptoms (Johnson et al., 2003). When morphine is used (as a tincture of opioid solution), lower dosages administered more frequently are associated with fewer days of hospitalization in comparison with higher dosages at longer dosing intervals [31]. An earlier (within the first three weeks), transient hyperphagic picture has been described which does not correspond to an increase in weight and appears to be unrelated to other withdrawal symptoms and maternal methadone dosage [49].

The relationship between NAS and maternal methadone dosage is controversial. Some authors have found no association with dose [4, 5, 24, 35, 37, 38, 42, 46, 51, 58, 64, 69], while other authors ascertained a dose-dependent relationship with regard to incidence and severity of abstinence in their samples [14, 26, 41, 47, 48, 50, 52, 53, 62, 63, 66]. Some of the studies evaluating this relationship used very low doses, far below average effective dosages. Such a methodological choice is likely to correspond to patients being treated at ineffective dosages and not representing the level of health and behavioural stability achievable by methadone maintenance. Anti-withdrawal and partially blocking dosages, such as those between 20 and 60 mg, do not suppress craving and favour the combination with other opiate-boosting or replacing drugs, such as benzodiazepines, leading to the misinterpretation of clinical findings. Patients, for whom a 20-30 mg dose is enough are likely to be low-severity individuals and will not abuse opiates during pregnancy; on the other hand, average-to-high-severity patients not provided with effective doses will continue abusing drugs when provided a 40-60 mg dose. In some studies, [10, 50], NAS severity is predicted by benzodiazepine and cocaine abuse, respectively, while no other opiate-related predictive factors are identified. The possibility of a combined withdrawal, (opiate and alcohol-benzodiazepines) may also be considered [57].

Therefore, NAS will tend to be more severe for higher dose patients, whose dosage is still not enough. However, no difference is reported by Berghella and colleagues, who studied NAS in infants exposed to less than 80 mg/day to those exposed to more than 80 mg/day [3]. Sinha et al [63] report NAS being more often in need of morphine treatment in women taking higher methadone doses, but methadone-only exposed children are at lower risk of NAS than heroin-exposed ones. Overall, most results indicate NAS is less frequent in infants of methadone treated mothers than heroin using peers. Although there is a risk of NAS in methadone exposed infants, the syndrome is treatable and not lethal if it is assessed and managed appropriately. The NAS is overshadowed by the acquired gain in pregnancy and delivery outcomes and the mother and child's health status as well as many psychosocial

aspects that can be ameliorated [29].

Many clinicians still practice medically supervised withdrawal from opioids during pregnancy [45]. Along the stated reasons for withdrawing pregnant women is to prevent NAS, prejudice or lack of knowledge about addiction and its clinical features [55]. Medical withdrawal is not indicated during pregnancy except in a few instances where logistics hamper the delivery of methadone maintenance.

Some clinicians have tried a fast detoxification procedure with the claimed aim of NAS prevention. A twelve-day schedule of methadone withdrawal shortly before birth resulted in 29% of relapses just after the schedule completion, and a global short-term abstinence rate of 59%, while 15% of newborns required treatment for a clinically relevant NAS [11].

Safe management of pregnant opioid addicted women should start by methadone maintenance at effective dosages. NAS resulting from methadone exposure should be evaluated by clinical surveillance and treatment when needed with an opiate at tapering doses [60]. Moreover, the administration of higher methadone dosages should never be offset by the priority to avoid neonatal withdrawal since NAS is manageable through adequate care and treatment, whereas damage resulting from untreated addictive behaviours can be permanent.

Opiate withdrawal can be effectively treated by following a tapering schedule [2, 56]. Shorter dosing intervals of opiate-containing solutions have been found to reduce the duration of withdrawal [9], Morphine solution is preferred for the treatment of NAS.

Breast feeding of mothers on methadone may be helpful in flattening the withdrawal slope to a drug-free state [21, 28, 44]. Breast-feeding alone is not likely to provide the infant with enough methadone supply, and is not always viable due to concomitant conditions, such as HIV infection. Barbiturate treatment may be indicated in addition to morphine when benzodiazepine withdrawal coexists.

6. Neonatal thrombocytosis

Increased platelet count and aggregating function have been reported in newborns of methadone treated mothers [6-8, 25], with an estimated prevalence of 3.65% [22]. A similar finding has been described in the offspring of opiate-tolerant female mice [7]. Platelet overcrowding may occur regardless of which opiate has been administered, that is both for heroin addicted mothers and opiate treated subjects. Its timing seems to follow that of neonatal opiate withdrawal, with a delayed onset one week after discharge and a protracted course lasting several weeks [22]. The causes and mechanisms of such a phenomenon have not been reported, however, the parallel evolution concomitant with the abstinence syndrome suggests it may be reversed by cross-tolerant opiate drug treatment.

7. Strabismus.

Surveillance for the development of strabismus is needed in children of opiate-dependent mothers. Available data do not indicate any correlation with either methadone dosage or altered opiate tolerance (NAS-related features) [23].

8. Methadone for pain in pregnant women

Chronic pain control may benefit from increased long-acting opiate coverage without employing further analgesic agents. Breakthrough pain control needs fast-acting agents. Morphine is suitable to relieve acute pain in methadone maintained patients with its dosage to be established on a subjective basis. As a rule, methadone tapering during pregnancy is not recommended. Pain can be one possible consequence of lowered opiate coverage. Other combinations with non opiate analgesics may be considered [61].

Women receiving methadone for pain control during pregnancy deliver earlier, differently from methadone maintained pregnant heroin addicts [23]. Methadone for pain is administered for shorter periods and generally at lower doses than that used for the addicted individual. NAS has been observed in 11% of the neonates. Wholly, neonatal outcomes of methadone treated pregnant women differ along the reason for methadone administration (pain vs. addiction).

9. Early child development

Developmental delays have been reported in methadone-exposed babies [55, 72]. Growth is slower during the first trimester, but no difference in achieved dimensions is noted at six months: a compensatory acceleration of growth takes place farther from discharge. Head circumference is normal within one year of age [40] while no cognitive delay is documented during infancy [36, 39, 40, 65]. However, when methadone is provided to pregnant women at effective dosages within structured programs, newborns tend to weigh more and have a larger head circumference; the latter in proportion with the average dose administered during the third trimester [24]. Examining the possible factors which may contribute to developmental abnormalities in a group of children of addicted mothers treated with methadone, no relationship was documented with opiate-related characteristics, such as methadone dose and duration of exposure to methadone [17].

10. Breast-feeding

Breast-feeding is possible for methadone maintained women. The milk contains approximately 2% of daily dose and concentration [71]. Values range from 0,05 to 0,57 mg/ml for dosages varying from 10 to 80 mg/day [71]. Daily methadone exposure is approximately 0,02-0,09 mg/die, far below the theoretical lethal dose in non tolerant babies. On

the other hand, such a dose is not enough to prevent NAS in opiate-tolerant newborns. However, methadone maintained mothers who breastfeed their babies should not stop abruptly if dosages are average-to-high [48]. A study linking prenatal methadone exposure to delayed development examined a group of women treated with an average dose around 40 mg, which does not shield against poly-drug abuse and addictive behaviours [70].

11. Psychological aspects

'Pregnancy', as a life event, is often experienced by patients, or suggested from others, as somehow psychologically linked with the natural history of addiction. Redemption themes should never be supported or induced, and pregnancy should never be considered as a healing opportunity through a withdrawal from therapy. In fact, expectations and motivational drives have nothing to share with the destiny of a metabolic disease. On the contrary, patients will have to be provided with adequate information on treatment opportunities and feasibility in order to complete pregnancy in the best way. A good counsellor could motivate, through the experience of treatment during pregnancy, a stronger relationship with the therapeutic program. In this case, pregnancy can really become a motivation to treatment and can be so turned into an "opportunity of treatment".

12. Parental role

Heroin dependence can compromise one's capacity to provide parental functions. The loss of maternal priorities in a heroin addicted woman with children allows us to understand its severity as a disease and its power to deviate behavior from instinctive and fixed patterns, such as that of maternal attachment to her infant. Feelings and emotions linked with the contact with and the responsibility for their children are often present in heroin addicted women. The incoherence between the importance that mothers claim to attribute to their children and their behavior, which is contrary to the maintenance of a parental role, is therefore an evident sign of addiction. Motherhood can represent in a woman who is a drug abuser but not drug addicted, an opportunity to stop her abuse, however, this is not the case in the presence of drug addiction. The awareness of their one parental responsibility and the presence of maternal feelings can cause in drug addicted mothers demoralization, guilt and feelings of inadequacy and suicidal thoughts. Maternal psychotoxic effects of abused substances expose children to the risk of a chronic lack of emotional interaction, neglect and abuse and experiences of violence in their environments. Drug addicted women are conscious of what could improve their parental function (i.e. a behavioral control recovery), but are not able to plan a coherent, adequate line of conduct. Drug addicted women, as with most drug addicted individuals

whose addiction is not very severe, aim to recover control of the substance of abuse, in order to continue its use freely, and resort to a treatment able to solve the critical situation of the moment. Questions such as home care or resorting to a family collaboration are considered secondary with respect to the solution of those linked with substance use. An anti-addiction therapy has to restore the mother so that she can maintain a parental role. Parental dysfunction is an expression of the disease of addiction and so its recovery has to pass necessarily through the treatment of the addictive disorder. As for every category of drug addicted individual, a therapeutic approach must have the aim of allowing patients to recover through a continuum between intention, planning and behavioral drives.

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Conflict of Interest

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