

# Effects of opioid agonist treatment for pregnant opioid dependent women

This is an excerpt from the full technical report, which is written in Norwegian.

The excerpt provides the report's main messages in English.

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We would like to thank all contributors for their expertise in this project. Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

Norwegian Knowledge Centre for the Health Services  
Oslo, November 2008

# Key messages

**Background:** The Norwegian Directorate of Health commissioned the Norwegian Knowledge Centre for the Health Services (NOKC) to do a review about the effects of opioid agonist treatment for pregnant opioid dependent women. The review would help answer the question of whether and how opioid dependence in pregnant women should be managed with the opioid agonists methadone and buprenorphine. The issue to be addressed was what kind of treatment effects methadone and buprenorphine medication caused during pregnancy on mother and child, compared to other or no treatment. We examined four effect questions: (1) Different dose levels of methadone; (2) Standard methadone maintenance treatment (MMT) versus enhanced MMT; (3) MMT versus other opioid agonist treatment (buprenorphine, slow-release morphine, Naltrexone implant treatment (NIT)); (4) MMT versus no medical maintenance treatment. We focused on the effects of such treatments on the opioid dependent women and their children.

**Methods:** In June 2007, we searched systematically for relevant literature in international scientific databases, selected studies according to pre-set criteria, appraised the methodological quality using checklists, and summarised the results in tables and in meta-analyses. We analysed the studies according to the four above mentioned foci.

**Results:** We included and summarised results from a total of 30 studies; four randomised controlled trials, one non-randomised clinical control trial and 25 non-randomised effect evaluations. Most studies were of medium or low quality and GRADE showed that the quality of the evidence was very low or low for all outcomes. With respect to dose level, there were too few studies and they were too heterogenous for us to perform any meta-analysis. This was true also for the question of standard versus enhanced MMT. With respect to the question of effect differences between MMT and buprenorphine, the meta-analysis showed that treatment with buprenorphine resulted in more mothers keeping custody of their children. However, GRADE documented very low quality for this outcome. According to our meta-analysis, methadone resulted in significantly fewer incidences of Neonatal Abstinence Syndrome (NAS) compared to slow-release morphine, but GRADE showed very low quality for this outcome. Lastly, with respect to effect differences between MMT and no medical maintenance treatment the meta-analyses showed that there were more cases of NAS among newborns of mothers receiving MMT compared to newborns of mothers receiving no treatment, and a longer treatment period was needed for these babies. However, women receiving MMT reported more prenatal visits, gave birth to babies with higher birth weight and gestation age, and these women were more likely to keep custody of their child compared to women receiving no treatment. GRADE showed very low quality for these outcomes.

**Conclusion:** The evidence base in this review was of very low quality and several questions could not be adequately answered. The current evidence base is insufficient to draw conclusions regarding the differential effects of various methadone dosages and standard versus enhanced MMT. Our meta-analyses suggested that there is an increased risk of NAS among newborns of mothers receiving MMT, and a longer treatment period is required. On the other hand, MMT led to some positive outcomes such as higher birth weight and parental custody. The evidence base included in this review was of low quality and the results are therefore tentative. There is an urgent need for more studies of high quality on the effects of medical maintenance treatment for opioid dependent pregnant women.

# Executive summary

## Effects of opioid agonist treatment for pregnant opioid dependent women

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### BACKGROUND

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The opioid agonists methadone and buprenorphine are the most common treatments for opioid dependence internationally (1). Specialists in several countries recommend medical opioid treatment (in Norway defined as medically assisted rehabilitation (LAR)) during pregnancy, or at least during parts of the pregnancy. This treatment involves possible negative effects such as Neonatal Abstinence Syndrome (NAS), reduced birth weight and possibly long term developmental and behavioural problems in the child. Likely positive effects is that the women early in pregnancy can be stabilized and enter into a collaboration with health workers about their own and their babies' welfare. Norwegian practice for treatment of pregnant women with opioid dependence using illegal drugs is detoxification and non-medical interventions, but there is an ongoing discussion about what treatment is preferable. This report will help to answer the questions whether and how opioid addiction in pregnant women should be managed with the opioid agonists methadone and buprenorphine. The main issue to be addressed is what kind of treatment effects methadone- and buprenorphine medication cause during pregnancy on mother and child compared to other or no treatment. We designed four questions:

1. What are the effects of different dose levels of methadone?
2. What are the effect of standard methadone maintenance treatment (MMT) compared to enhanced MMT?
3. What are the effects of MMT compared to other opioid agonist treatments (buprenorphine, slow-release morphine, and Naltrexone implant treatment (NIT))?
4. What are the effects of MMT compared to no medical maintenance treatment?

The present review was commissioned by the Norwegian Directorate of Health.

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### METHODS

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In June 2007 (with a supplemental search in September 2008), we searched systematically for relevant literature in the international scientific databases The Cochrane Central Register of Controlled Trials (CENTRAL), OVID MEDLINE, OVID EMBASE, OVID PsycINFO, and OVID CINAHL. In addition, we examined reference lists in relevant systematic reviews to identify single studies that we might otherwise have missed. Two reviewers independently evaluated studies for inclusion using a pre-designed inclusion form, and then appraised the methodological quality of the included studies with appropriate check lists. We summarised the studies in tables and in meta-analyses. We organized the studies within four groups, in accordance with our review questions: Effects of dose levels of methadone; Effects of standard MMT versus enhanced MMT; Effects of MMT versus other opioid agonist treatments; Effects of MMT versus no medical maintenance treatment.

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## RESULTS

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We included 30 studies; four randomised controlled trials, one non-randomised clinical control trial and 25 non-randomised effect evaluations (observational studies). Most studies (84%) were of medium or low quality, GRADE showed that the quality of the evidence was very low or low for all outcomes. About half of the studies were from year 2000 or more recent, and slightly more than half (55%) were from the US. With respect to question one, which dealt with dose levels, three studies met our inclusion criteria. These were too heterogenous for us to perform any meta-analyses. This was true also for the question of effects of standard versus enhanced MMT, though the two individual studies included showed more positive results for prenatal visits and birth weight when the mothers received enhanced MMT. For question three, which examined the effects of MMT versus other opioid agonist treatments, we included nine studies. Our meta-analysis of seven studies about the effects of MMT versus buprenorphine suggested that treatment with buprenorphine resulted in fewer premature births and more mothers kept custody of their children, compared to MMT, but GRADE showed very low quality for these outcomes. We included four studies about the effects of MMT versus slow-release morphine treatment and the results indicated that MMT is preferable to morphine when it comes to NAS, but GRADE dosumented very low quality for the outcome. We included 15 non-randomised effect evaluations that assessed the effects of MMT versus no medical maintenance treatment. According to the meta-analysis, there was a higher incidence of NAS among newborns of mothers receiving MMT compared to those of mothers receiving no treatment, and longer treatments were needed for these babies. On the other hand, women receiving MMT attended more prenatal visits, gave birth to babies with higher birth weight and gestational age, and these women were more likely to maintain custody of their child compared to mothers receiving no medical maintenance treatment. However, GRADE showed very low quality for these outcomes.

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## CONCLUSIONS

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There was great variation among the 30 included studies in quality, outcomes, and how the results were presented. These variations, coupled with an evidence base of very low quality and few long-term follow up studies make it difficult to form an empirical basis for drawing solid conclusions about the questions asked in this report. The current evidence base is insufficient to draw conclusions regarding the differential effects of various methadone dosages and standard versus enhanced MMT. Our meta-analyses suggested that there is an increased risk of NAS among newborns of mothers receiving MMT, and a longer treatment period is required. On the other hand, MMT led to some positive outcomes such as higher birth weight and parental custody. Given the very low quality of the evidence base, the results presented in this report are tentative. There is an urgent need for more studies of high quality on the effects of medical maintenance treatment for opioid dependent pregnant women.