

Review of evidence

What is the knowledge base for tapering from methadone or buprenorphine during pregnancy?

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0.1 Norsk sammendrag

Bakgrunn: Legemiddelassistert rehabilitering (LAR) blitt også gitt til gravide. Abstinenser og muligens også andre negative effekter kan observeres i nyfødtp perioden. Kan nedtrapping av opioider i svangerskapet være et alternativ?

Mål: Vi undersøkte utfall hos fosteret og for den nyfødte av det å trappe ned opioider under svangerskapet. Vi så også på utfall hos moren under og etter svangerskapet. Kunne vi finne karakteristika ved mødrene eller kjennetegn ved behandlingen som økte sjansene for en vellykket nedtrapping? Til sist skulle vi si noe om kunnskapshull.

Materials: En systematisk litteraturgjennomgang ble gjennomført i databasene MedLine, Embase, Cinahl, Cochrane og PsychINFO. I tillegg ble det gjennomført et manuelt søk. Vi fant 268 mulig aktuelle vitenskapelige artikler. En gjennomgang av titlene resulterte i 96 artikler ble beholdt, mens en videre gjennomgang av sammendragene resulterte i at 46 artikler ble beholdt. Alle disse ble gjennomgått i fulltekst og referanselistene til disse artiklene ble også gjennomgått. Sluttresultatet var 20 artikler som omhandlet 5 kasusbeskrivelser og 14 ulike studier (én studie ble omtalt i to ulike artikler).

Metode: Alle de inkluderte vitenskapelige artiklene ble nøye lest og vurdert for å se om de kunne besvare spørsmålene.

Resultater: *Konsekvenser for fosteret* av nedtrapping ble omtalt i 3 kasusbeskrivelser og 4 observasjonelle studier. De tidlig publiserte kasusbeskrivelsene problematiserte intrauterint stress og beskrev én dødfødsel. De senere observasjonelle studiene kunne imidlertid ikke å vise en overhyppighet av intrauterin død enten fordi dette ikke ble undersøkt, fordi de ikke hadde statistisk styrke eller fordi effekten ikke var der. *Utfall for det nyfødte barnet* ble beskrevet i 9 ulike vitenskapelige artikler fra 8 studier. Til tross for dette antallet studier var det ingen som hadde undersøkt eller dokumentert konsekvenser for den nyfødte. Studiene viste at det som betyr noe for utfall ved fødsel har mest å gjøre med mors bruk av rusmidler eller LAR ved fødselen. Mer bruk av LAR-legemidler eller rusmidler ga større konsekvenser. Studiene viste at det å trappe ned var vanskelig, men kan klares med støtte. Undersøkelser av *faktorer ved mor* som kunne bidra til en vellykket nedtrapping (som målt ved avholdenhet fram mot fødsel) kunne ikke identifisere noen spesielle kjennetegn. Avholdenhet fram mot fødselen var først og fremst relatert til av graden av omsorg eller kontroll med mors situasjon.

Diskusjon: I denne systematiske gjennomgangen av konsekvensene av nedtrapping av opioider i svangerskapet må all diskusjon føres med forsiktighet på grunn av det begrensede kunnskapstilfanget. Tidligere studier indikerte stress for fosteret etter nedtrapping, men det er en mangel på systematiske studier om dette utfallet. Intrauterin død har blitt beskrevet, men det har ikke vært mulig å bekrefte en forhøyet risiko. Dette kan komme av for små studier med manglende statistisk styrke. Ingen studier har sett på fødselsutfall etter nedtrapping, men det er klart at den viktigste faktoren for fødselsutfall er morens avholdenhet ved fødselen. Det er vanskelig men ikke umulig for mor å trapp ned opioider. Det springende punktet er imidlertid om hun klarer å holde seg fra rusmidler fram mot førselen. Dette avgjøres først og fremst av graden av omsorg og kontroll, uten at litteraturen spesifikt angir hva som er en tilstrekkelig grad av omsorg eller kontroll. Nyere studier om nedtrapping av kvinner som er avhengige av forskrevne opioider kan øke vår kunnskap og gir noen grunn til optimisme med hensyn til muligheten for nedtrapping under svangerskapet, men denne gruppen pasienter er annerledes og det er for tidlig å si om kunnskapen fra denne gruppen lar seg overføre til LAR-pasienter. Ny kunnskap trengs i grunnen å alle områder innen dette feltet.

0.2 English summary

Background: Opioid maintenance treatment (OMT) is also given to pregnant women. Neonatal abstinence syndrome and possibly other adverse events can be observed in the neonatal period. Could tapering of opioids during pregnancy be a better alternative?

Aims: We investigated fetal and neonatal outcomes of tapering during pregnancy. We also looked at maternal outcomes of tapering during pregnancy and whether any maternal or treatment characteristics for successful tapering could be found. Lastly we pointed out potential gaps in the research.

Materials: A systematic literature review was performed in MedLine, Embase, Cinahl, Cochrane and PsychINFO databases in addition to a manual search. This search captured 268 scientific publications. Reviewing titles left us with 96 papers. Reviewing abstracts left us with 46 reports. These were read in full text and their reference lists were also searched manually for additional publications. This left us with a total of 20 contributions consisting of 5 cases and 14 studies published in 15 papers.

Methods: All included papers were read and scrutinized for data that could answer the research questions.

Results: *Fetal consequences* of tapering of opioids during pregnancy were described in 3 cases and 4 observational studies. The early cases problematized fetal distress and described intrauterine deaths, but the observational studies failed to confirm this, either because the harmful effects described in the cases were not investigated or because an increased rate of intrauterine death could not be demonstrated, although this could be a question of statistical power. Results on *neonate consequences* of tapering during pregnancy were described in 9 papers based on 8 studies, but were still scarce and too limited to describe any neonate consequences specific to tapering. Rather, the studies described neonate consequences following the drug use of the mothers at birth, whether legal (OMT) or illegal drugs. More drug use led to greater consequences. Studies show that tapering is difficult, but can be managed with support, also with the use of medicinal drugs. Investigations on *maternal factors* shows that success of the tapering (as measured by continued abstinence) depends mostly on the degree of care and control after tapering, with a higher chance of success where there

is a high degree of care and control. No studies address possible maternal factors that increase the chance of successful tapering.

Discussion: In this systematic review of the consequences of tapering opioids during the pregnancy, all discussion must be cautious because of the poor empirical evidence base. The early case studies indicated fetal distress after tapering, but there is a lack of systematic investigation concerning such outcomes. Intrauterine death has been described, but larger studies have not been able to confirm any heightened risk. This may be due to a lack of statistical power. No studies highlight neonatal effects after intrauterine tapering, the most important factor being the mother's degree of abstinence from drugs at the birth. Albeit difficult, mothers are able to taper with assistance from drugs. The crucial point is whether they are able to stay abstinent after tapering. This cannot be achieved without proper follow up. The degree of care and control is crucial, but other literature need to be reviewed to determine what level of care or control is sufficient. Newer studies on tapering in women abusing prescription opioids may increase our knowledge and give reason for optimism regarding sustainable abstinence after tapering, but the transfer to OMT-patients has not been determined. New research would be welcomed on any aspect of this topic.

1. Background

The introduction to this review will be kept short as much of the background literature will be reviewed by other parties also performing reviews for the similar consensus conference (see chapter 2: material and methods).

The introduction of opioid maintenance treatment (OMT) for individuals with heroin addiction has proven a success for many treatment outcomes such as retention in treatment and reduced heroin use (1-3), HIV risk and criminal behaviour (3), mortality (4) and somatic health (5). Obviously young female patients of fertile age are also given this treatment, with the inherent risk that they may become pregnant. Many of these pregnancies are unplanned (6), but the increased life quality of these women may increase their desire and ability to become mothers. Adequate advice on family planning and use of contraception should be given (7), but still babies of women in OMT will be born. Many of these babies experience neonatal abstinence syndrome (NAS) indicating that they have developed tolerance to opioids *in utero* and thus experience withdrawal after birth (8). Some other negative outcomes have also been seen such as pre-term birth and low 5-minute APGAR scores (9) and others have been speculated on such as visual, motor, and behavioural/cognitive problems (10). The NAS symptoms can be treated, but have still been experienced as dramatic by those observing them, including health personnel (11). Some professionals have spoken vigorously out against the practice of giving OMT to pregnant women on these grounds. It has, however, been argued that when adequate contraception and advice about contraception has been given (7), women cannot be prohibited from becoming pregnant and that tapering the women without proper follow up is often a worse alternative. Also, are we sure that the fetus is better off being tapered *in utero*, compared to what is experienced in the neonatal phase (12, 13)? Or is this just a matter of being more comfortable with what you do not see? It could be that the consequences of neonatal tapering are much worse than the consequences of intrauterine tapering. But the opposite could also be true.

This is some of the background for the current literature review. The aims of this systematic review were set by the Norwegian Directorate of Health in their commission to the author. They wanted a

review to shed light on the following issues (figure 1 illustrates some of the relationships in this review):

- A. Tapering of OMT medication (or other prescription opioids) should be compared to continued OMT during pregnancy. What are the neonatal and longer term outcomes for the child? What are the maternal outcomes?
- B. How is the safety of the fetus and the woman, respectively, secured during tapering compared with women who continue OMT throughout pregnancy?
- C. What are the patient characteristics for successful tapering? (success = the woman remains free of medication and other substance use after tapering)
- D. What kind of additional treatment increases the probability of successful tapering?
- E. What are the gaps in the research?

2. Materials and methods

2.1 Materials

The papers for this systematic literature review were gathered in several steps. Firstly two manual, unsystematic searches for literature were performed by the author and a colleague (Dr. Gabrielle Welle-Strand). These searches identified 38 potential papers (fig. 2). Secondly a request was sent to the research library at Innlandet Hospital Trust, Hamar for a search. The search strategy with terms used by the library is found in the appendix (chapter 8). They compiled a search from five different databases (MedLine, Embase, PsycINFO, Cinahl and Cochrane). The literature search was carried out at the end of January 2017.

The results of the database search were compared to the original manual search results and it was found that many of the potentially relevant papers from the manual search were missed. Too many review papers and too many papers including tapering of e.g. tobacco were included. Thus, a new Medline search was performed very close in time to the first search, also ending in the last days of January 2017.

On the basis of these 6 systematic searches (2 in Medline, 1 in Embase, 1 in PsycINFO, 1 in Cinahl and 1 in Cochrane) and on the basis of the original manual search, a file of 268 possible papers were listed in a table (see appendix, chapter 8). The titles of these papers were reviewed for acceptability. This left us with 96 papers that were believed to be relevant (see list in appendix). Of these 28 were from the manual search, 10 from the first Medline search, 7 from the Embase search, 37 from the PsycINFO search, 7 from the Cinahl search, 7 from the Cochrane search and 45 from the second search in Medline).

These 96 papers were reviewed in abstract. Studies obviously not containing any mention of tapering in pregnancy were disregarded (N=43). Likewise all animal studies were taken out (N=6). Two abstracts were deemed to be the same. Altogether 45 papers and one monograph were read in full text.

All kinds of papers: cases, case series, observational studies, intervention studies, commentaries, letters-to-the-editor or editorials were included among the papers that were read in full text. This was done to ensure that we also could spot other empirical evidence in the reference lists of these papers that may not have been captured by the systematic search in the databases.

On the basis of reviewing the 46 papers, 10 papers were deemed highly likely to contain relevant information and an additional 5 papers were thought possibly to include relevant information. Reviewing the reference lists of these 15 papers we found an additional 33 papers that were then reviewed. Of these 33 papers, 10 were deemed to be of relevance and an additional 3 had possible relevance, leaving us with 28 papers that were scrutinized more thoroughly. This thorough reading made it clear that 4 papers were not relevant (one thought to be relevant, but turned out to be on outcomes in older children (14)). Of the 24 papers left we found that (fig. 3) 5 were relevant cases, 15 were relevant studies (although it was a bit unclear if two studies contained the same information published in two journals (15, 16); these two papers by Jones et al – both from 2008 were, in the following, reviewed together) and 4 other papers included patients tapered, but no separate information was given on the tapered cases separately. All in all 5 cases and 14 studies (in 15 papers)

with observational data were included in the final review. An overview of these papers is given in table 1.

2.2 Methods

This review was created for the Norwegian Directorate of Health as a contribution on a specific theme for their consensus conference on OMT in pregnancy to be held in June 2017, as a preparation for a national consensus report being published in 2017. The strategy and limits of the review were discussed with the Directorate in several emails and also in a meeting with the other parties contributing to the same conference. Specifically it is noted here that another review of animal studies will be carried out (led by Dr. Jannicke Andersen) so this review will not include animal studies. Neonatal outcomes in babies of non-tapered women will be covered by yet another review (led by Dr. Gudrun Høiseth). An overlap between these three reviews could occur e.g. where women are partially tapered and give birth with lower doses. In this case dose vs. neonatal outcome will be left to Dr. Høiseth's review while fetal outcomes of any tapering, even if not to zero, will be covered by this review.

The results of the studies will be reviewed in detail, mentioning all studies under the headings "Fetal effects" (still births/miscarriages/fetal demise) and other fetal outcomes, "Neonate effects" (gestational age, birth weight, birth length, APGAR score 1 and 5 minutes, head circumference, neonatal abstinence syndrome (NAS)) and "Maternal effects" (relapse, drug use) in the results section.

In the review, "tapering" is used both for detoxification and tapering terms used in original papers. In many studies, the term detoxification is used not only for going off drugs all together, but also for those patients going off illegal drugs to maintenance drugs. In the review, these maintained patients are not considered as tapered/detoxified. Intrauterine death will be referred to as such regardless of whether it is a fetal demise, still birth (dødfødsel) or miscarriage (spontanabort).

3. Results

3.1 Fetal effects

Four observational cohort studies have been published:

Study 6 (17) observes 2 miscarriages in a cohort of 301 after tapering in first trimester (N=28).

Study 62 (18) observed the prevalence of intrauterine death after tapering in a cohort of 111 pregnancies, identifying 1 intrauterine death after tapering in the first trimester (OR 6.87, NS), no intrauterine deaths in the second trimester and 1 intrauterine death after tapering in the third trimester (incidence equal to the population level).

Study 101 (19) reports one intrauterine death in tapered women. The drug use status at the time of the incident is unclear, but probably relapse.

Study 161 (20) observed an intrauterine death after tapering in the second trimester in a cohort of 33 pregnancies.

3 case studies have been published shedding light on fetal distress:

Study 99 (21) investigated levels of epinephrine and norepinephrine from amniotic fluid of a pregnancy of a mother who was tapered from methadone and showed a sharp increase in stress hormones (epinephrine and norepinephrine).

Study 309 (22) observed possible problems with umbilical blood flow following tapering, normalizing after methadone maintenance.

Study 310 (23) describes an intrauterine death after tapering in the third trimester. The risk of Intrauterine death is elevated with amniocentesis but not greatly and perhaps less than previously thought, but it is still present (24).

Review 102 introduces the concept of intrauterine abstinence syndrome (IAS). However another study points out that there are few viable measures (12). The usefulness of the concept is criticized by others (study 300/311 (13)), but they use only neonate data to support this criticism.

3.2 Neonate effects

Study 6 (17) compares 3 groups with full control (108), less control (116) and little control (77) respectively after tapering and monitored rates of relapse (mentioned under maternal effects) and rate of NAS, finding that moderate to high control/follow up after tapering is related to less NAS. NAS follows the rate of relapse.

Study 8 (25) describes 8 successfully tapered (helped by methadone) women compared with methadone or buprenorphine maintained women. The babies of the women that had successfully withdrawn showed a lower NAS peak and had less need of treatment for NAS. For all other birth outcomes (gestational age, weight, height, Apgar score etc.) there were no differences.

Study 13 (26) included few babies born of fully tapered women, but many of the women had decreased their OMT doses > 50 % (21/123 = 17 %; this group contained some fully tapered women)

and the women who had reduced their opioid doses the most gave birth to children with a higher birth weight.

Study 22 (27) compares two cohorts of substance- using patients: one out-patient (N=78) (little control) and one inpatient (N=21, 13 voluntary, 8 involuntary) (more control). The study finds higher gestational age, birth weight and head circumference among the tapered and controlled inpatients.

Study 26 (28) compares 53 drug free (tapered) women with 42 illicit drug users at delivery, where 9 % vs. 33 % of the mothers left the tapering programme prior to completion. There were fewer NAS and less treatment needed, higher gestational age and higher birth weight among the successfully tapered births.

Study 50 (16) and study 142 (15) are from the same clinical study by Hendrie Jones and co-workers. In this study 95 tapered patients were compared to 80 methadone maintained patients. Only one of the studies focused on the neonatal outcomes (13). The other on maternal outcomes (15). The tapered (but not abstinent) women gave birth to children with possibly lower head circumference and requiring more care in intensive care unit. There was no difference in prevalence of NAS (16).

Study 89 (29) studies outcomes of pregnancy in 17 tapered women compared to 8 woman using methadone, vs. 52 other women. It shows higher gestational age, birthweight and greater head circumference and possibly less NAS in those successfully tapered and maintained without use of opioids.

Study 167 (30) describes 30 tapered and drug free women living in sheltered prenatal care compared to a diverse control group. The study found the tapered group to have higher birth weight and shorter nursery stays post-partum.

3.3 Maternal effects

Study 6 (17) observed relapse rates in several groups of tapered women (N=301) ranging from 17 % relapse in prescription opioid addicted women followed in an intense behavioural health programme involving activity at least 8 hours per day (N=23), to 23 % relapse rate among incarcerated women (N=108) and similar in women followed in a less intense continued behavioural health follow-up (N=93), to 73 % relapse rate in the group with little follow-up (N=77).

Study 13 (26) observed 123 women who tried to taper during pregnancy. Most did not taper, but 21 (17 %) managed to taper more than 50 % of original dose, and two came off fully. No specific characteristics of the mothers who were able to taper were found except that these mothers less often smoked (67 % vs. 83-92 %).

Study 15 (31) followed 86 tapered mothers, but only 8 (9 %) were off drugs at birth. Most measures are between those in the tapered group (with varying degrees of taper), making it difficult to take any empirical knowledge from this study. No difference was seen between drugs used to taper.

Study 19 (32) is a case story of a woman trying (but not succeeding) to taper, illustrating the difficulties with tapering.

Study 22 (27) does not show any maternal outcomes except for drug use in both second and third trimester, where the mothers in residential treatment had significantly less use of most drugs including nicotine.

Study 26 (28) compared 53 women (56 %) who were successfully tapered with those who were not successful in quitting drug use (N=42), but the study failed to identify success criteria for tapering, except that HCV was less frequent among those who were successful (40 vs. 64 % HCV positive). The authors underline the time and commitment that must go into tapering efforts.

Study 50 (16) compares 95 tapered women with 80 methadone maintained women. The tapered women more often had positive urine toxicology at delivery (53-7 % vs. 15-33 %). The groups were not directly comparable as the tapered (but not maintained) women were more often non-white, had fewer treatment episodes previously, and used more cocaine. Study 142 (15) is from the same cohort and has no additional findings.

Study 75 (33) is a case history revealing no specific success criteria for tapering.

Study 77 (34) compares 20 tapered women with 10 continued illegal opioid users and 4 methadone maintained women, finding few if any differences.

Study 89 (29) compared 17 tapered women with 57 others, but few results on mothers are clear for the tapered group exclusively, although one result could point in the direction of less positive urine screen at time of delivery.

Study 161 (20) describes a study that uses clonidine for tapering of drug abusing mothers. 23 of 33 managed to taper. No specific characteristics are given of the subjects who did not manage complete tapering.

Study 167 (30) gives data on 30 pregnancies of women in residential care and 44 controls, giving information on birth outcomes. Little information is given on the residential care except that the care is comprehensive, and no specific characteristics of the females included in the care are given.

4. Discussion

Our main finding and overall impression is that there is a great paucity of studies on the many difficult and intricate problems inherent in this field. The questions asked by the Norwegian Directorate of Health to this systematic review were ambitious, and in many ways too ambitious for the literature to answer. Also in the course of carrying out this systematic review the author has come to the conclusion (to a large extent because of the scarce empirical evidence available, but also from a theoretical point of view) that the order and the wording of the aims must be slightly changed. The new aims of this systematic review are thus reformulated

1. What are the fetal outcomes of tapering during pregnancy?
2. What are the neonatal outcomes of tapering during pregnancy?
3. What are the maternal outcomes of tapering during pregnancy? Are there any maternal or additional treatment characteristics for successful tapering?
4. What are the gaps in research?

In addition to answering these research questions the discussion will also touch on the original question asked by the Norwegian Directorate of Health.

4.1 What are the fetal outcomes of tapering during pregnancy?

A case study from 1973 described a still birth after tapering in the third trimester (23). This study and some additional studies (21, 35) resulted in years of scepticism towards tapering (16, 36). Three later observational cohort studies, however, found only two intrauterine deaths after tapering of 28 opioid addicts in first trimester (17), one intrauterine death after tapering in the second trimester in a cohort of 33 pregnancies (20) and one intrauterine death after tapering under unclear circumstances (5). Only one study has tried to quantify the risk (18). They investigated the prevalence of miscarriage after tapering in 111 pregnancies, identifying 1 miscarriage after tapering in the first trimester giving an odds ratio (OR) of 6.87, but this was a non-significant result with a wide 95 % confidence interval ranging from 0.16 to 47.3 due to the small size of the observed group. No miscarriages took place in the second trimester after tapering and one miscarriage after tapering happened in the third trimester, but this gives an incidence rate equal to the population level.

A commentary paper from 2012 introduced the concept of intrauterine abstinence syndrome (IAS) (12). This can in many ways be a useful concept, as it verbalizes the fear that the consequences for the fetus are just as bad as for the neonate. We should question if this abstinence could be just as harmful as neonate abstinence syndrome (NAS) and whether it is not just preferred because it cannot be observed by us. However, as the commentary itself points out, there are problems monitoring intrauterine abstinence syndrome, and, as yet, no good studies with viable measures (12). The usefulness of the concept has thus been questioned (13). The issue remains unresolved. Two cases introduce some possible measures indicating the presence of IAS, but they are only cases. One case investigated levels of epinephrine and norepinephrine from amniotic fluid of a pregnancy of a mother that was tapered from methadone showing a sharp increase in stress hormones (epinephrine and norepinephrine) (21). The other observed possible problems with umbilical blood flow following tapering, normalizing after methadone maintenance (22). So IAS cannot be ruled out, but no good studies or feasible measures have been identified.

So, there are too few studies on the safety of the fetus when tapering during pregnancy to draw any definite conclusions. There are some worrying case reports (21-23) and examples from observational studies of intrauterine death (17, 20), but the one study comparing rates with population levels found no significant increase (18). More studies are, of course, needed. The study by Bell and co-workers is, in this respect, interesting as it suggests that the current opioid epidemic in USA could provide more information (17, 37), and they go far in suggesting that the new information from such studies will prove the feasibility of tapering during pregnancy. But they underline the necessity of intense follow up. It has been suggested that animal studies could provide more basic information, but the external validity of animal studies on these issues is questionable. Further information on this will probably be given by the review of animal studies performed by Dr. Jannicke Andersen.

4.2 What are the neonatal outcomes of tapering during pregnancy?

There are more studies on outcomes in the neonate than in the fetus. The studies of new-born children of tapered women show that neonatal outcomes are highly dependent on the mothers' use of drugs at birth. Thus when studies compare tapered and non-drug using mothers vs. mothers using illicit drugs (26, 28, 30, 34) or being maintained on OMT (25, 29), we most often see less NAS (25, 28, 29, 31) and in most studies higher gestational age (28, 29) and birth weight (26, 28-30), greater head circumference (29) and shorter nursery stay (30). Degree of control of the women after tapering seems to predict opioid or other drug use when giving birth (see next chapter) illustrated by the fact that neonatal outcomes are closely related to drug use at birth. Thus tapering followed by total or high degree of control vs. tapering followed by less or no control leads to babies born with less NAS (17), higher gestational age and birth weight and larger head circumference (16, 27).

We found no studies following up on long term outcomes for children born after intrauterine tapering. Long term outcomes for children are very closely related to maternal outcomes that influence childhood environment.

In conclusion it seems that neonate outcomes after tapering are, to a large extent, related to the mother's drug use at delivery (34), whether this is illegal drug use, or reinstatement of substitution treatment. No studies addressed whether the tapering as such gave rise to neonatal effects. This could be because so many other factors influence neonatal outcomes, that any (smaller) effect of the tapering will be lost in larger factors. It is difficult to ascertain what kind of research would help enlighten this field. As mothers' drug use at delivery is of such importance, reference should also be made to Dr. Gudrun Høiseth's review on neonatal outcomes.

4.3 What are the maternal outcomes of tapering during pregnancy? Are there any maternal or additional treatment characteristics for successful tapering?

Some of these studies focus on how to taper the women (20), but the focus of this review is on the degree of relapse to drug use in different regimes (which by some is viewed as the major obstacle (38)). We wanted to identify any characteristics of the women or the treatment settings that could predict a higher success rate of tapering.

Voluntary tapering of opioids is difficult, even for pregnant women. Out-patients have difficulties in going off drugs even with supported tapering and some reviewers recommend hospitalization (39). This is illustrated by success rates ranging from as low as 1 % (26) to 9 % (31). These difficulties are

supported by case stories (32, 33). It is difficult to judge by the papers the degree of commitment from the women or the degree of coercion involved in the settings. However, quite a few women are able to reduce their use of OMT medication (26). It is possible (although no comparative studies have been done) that tapering with clonidine is easier (20), while others point to methadone tapering (15, 16, 25). Successful tapering and maintained abstinence predictably leads to fewer positive urine screens at time of birth (29).

It has been difficult to identify specific characteristics of those pregnant users that have more success with tapering (28, 31, 34), except possibly smoking is less prevalent among those succeeding (26) or maybe fewer HCV infections among those successful in tapering (28). Smoking is a hard habit to break so this may indicate more determined women. Being HCV-negative may be a sign of less marginalization (Or years and severity of opioid addiction linked to use of heroin and other injectable drugs), but as the most striking finding is that no specific features are identified, it would be wrong to draw conclusions from two, possibly spurious findings.

Some information exists on the type of care needed to maintain abstinence after tapering. Some studies only state that the care must be comprehensive (28, 30), with interdisciplinary cooperation many hours per day. Some suggest residential treatment and found that it led to less illicit drug use (27), but others find that even out-patient treatment with intense behavioural health programs (activity at least 8 hours per day) can also reduce relapse rates, even comparable to what we find in incarcerated women, and far better than in those with little or no follow up (17).

Only two studies were found that compared continued OMT vs. tapering. One had a slightly unclear data presentation, but found few differences (34). It was difficult to determine the degree of drug use and level of control of the tapered women. The other study, among 95 tapered women compared with 80 methadone maintained women, gave quite clear results, indicating that the tapered women more often had positive urine toxicology at delivery (53-7 % vs. 15-33 %). The groups were, however, not directly comparable as the tapered (but not maintained) women more often were non-white, had fewer previous treatment episodes, and used more cocaine (15, 16).

In conclusion these studies illustrate that tapering of opioid, be it OMT or other, is not easy, and professional help and support is needed. This is said even if there is a clear publication bias towards describing those who need help. The crux is, however, whether the tapered women (from illegal opioids or OMT) are able to stay off drugs after the tapering, as pointed out by some reviewers (36). The clue here is degree of follow-up and control. Several studies show that low follow up and control leads to increase in drug intake at birth (15-17), but a higher degree of success is found with intensive follow up (17), residential treatment (27) or even imprisonment (17). We found almost no information on characteristics of the women who had more success, suggesting that this is not such an important issue, but of a degree of motivation seems to be important. This point need to be discussed further. Could an increased use of different resources help? Norway has earlier been criticized for the use of coercion against pregnant drug users. Should this still be done, as control is such an important factor?

4.4 Research gaps

The research questions within this systematic review are timely, but to a very little degree answered by the current research. All fields could benefit from better investigations. The current review points

all these research gaps. If resources were to be put into research it would probably be wise to invest them in looking at

- fetal distress after tapering with more sophisticated methods and
- what would be sufficient follow up to keep mothers abstinent.

Research into the fields of

- maternal characteristics that would assure more successful tapering interventions,
- neonatal consequences of tapering during pregnancy or
- more long term consequences of tapering during pregnancy

are much more difficult to perform and results may be more difficult to obtain

5. Acknowledgments

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7. Tables and figures

Table 1. An overview over the 23 studies that contained empirical results and were used in the study

Running internal ID (reference list #)	Reference	Year	Type of study, material and taper N	Other maternal outcomes	Fetal outcomes	Neonatal outcomes	Final conclusion on relevance
6 (17)	Bell et al	2016	T 301, full control (108) vs. moderate control (116) vs. little control (77)	Preterm deliveries (NSi)/relapse	NSt	NAS	Relevant observational study
8 (25)	Lund et al	2012	T 25 vs. B 5 vs. M 12	several	NSt	Less NAS	Relevant observational study
13 (26)	Welle-Strand et al	2015	Observation of 123 P (M 80, B43), 75 tried to taper: 2 off, 19 > 50 % vs. 30 less vs. 24 no taper (+ 48 did not try)	NSt	NSt	Higher BW with reduced doses	Relevant observational study
15 (31)	Dooley et al	2015	T 86: the study has only some data on the success of tapering (for other measures, not good distinction)	8 (9.3%) of tapered stayed off			Relevant observational study
19 (32)	Welle-Strand et al	2014	Case: not fully T	Back on B			Case
20 (40)	Kelly et al	2014					Tapering included but no separate data
22 (27)	Haabrekke	2014	T 21 (8 involuntary) vs. 78 out-patient	NSt	NSt	Gestational age, weight, head	Relevant observational study
26 (28)	Stewart et al	2013	T 96 success (53) vs. others (43)	Success longer T stay	NSt	Less NAS	Relevant observational study
50 (16)	Jones et al	2008	Observational (95 tapered vs. 80 M)	+ urine (M: 21%, T: 43%)	NSt	Several	Relevant observational study
62 (22)	Luty et al	2003	Comparing incident rates of		miscarriage		Relevant

			miscarriage depending on when tapering from heroin was done				observational study
75 (33)	Annitto	2000	Case: heroin addict tapered on B	NSt	NSt	NSt	Case
77 (34)	Dashe et al	1998	Observation of 34 P (mostly heroin), 10 relapse (5 after taper), 4 on M, 20 success	10 relapse (5 after taper), 4 on M	NSt	NSi	Relevant observational study
89 (29)	Maas et al	1990	T 17 M 8 other 49	toxicology	NSt	Several	Relevant observational study
99 (21)	Zuspan et al	1975	Case		Measures of E and NE I amniotic fluid		Case
101 (19)	Blinick et al	1969	100 tapered, many returning to heroin use; difficult to ascertain differences between abstinent and non-abstinent		1 intrauterine death		Relevant observational study
142 (15)	Jones et al	2008	Observational (95 tapered vs. 80 M) (same study as #50?)	+ urine (M: 21%, T: 43%)	NSt	Several	Relevant observational study
161 (20)	LePreau et al	1995	T 23/33	Some (leaving early, relapse)	miscarriage	NSt	Relevant observational study
167 (30)	Kyei-Aboagye et al	1998	T 30 selected vs. 44 still abusing	NSt	NSt	Weight	Relevant observational study
309 (22)	Wong et al	1997	Case: intrauterine withdrawal		Effects of blood flow in umbilical cord		Case
310 (23)	Rementeria et al	1973	Case: stillbirth after T		stillbirth		Case
315 (41)	Connaughton et al	1977	Some tapered and non-drug using mothers, but data not given on this subgroup separately				Tapering included but no separate data
317 (42)	Harper et al	1974	6 tapered and non-drug using mothers, but data not given on this subgroup separately				Tapering included but no separate data
319 (43)	Rosen et al	1976	Some are tapered, but no data given				Tapering included

			on this subgroup separately				but no separate data
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NSt = not studied, NSi = non-significant, P = pregnancy, M = methadone, B = buprenorphine, BW = birth weight, T = tapering/detoxifying, NAS = neonatal abstinence syndrome, E = epinephrine, NE = norepinephrine, IAS = intrauterine abstinence syndrome

Figure 1. A graphic illustration of the relationships between the investigated exposures and outcomes

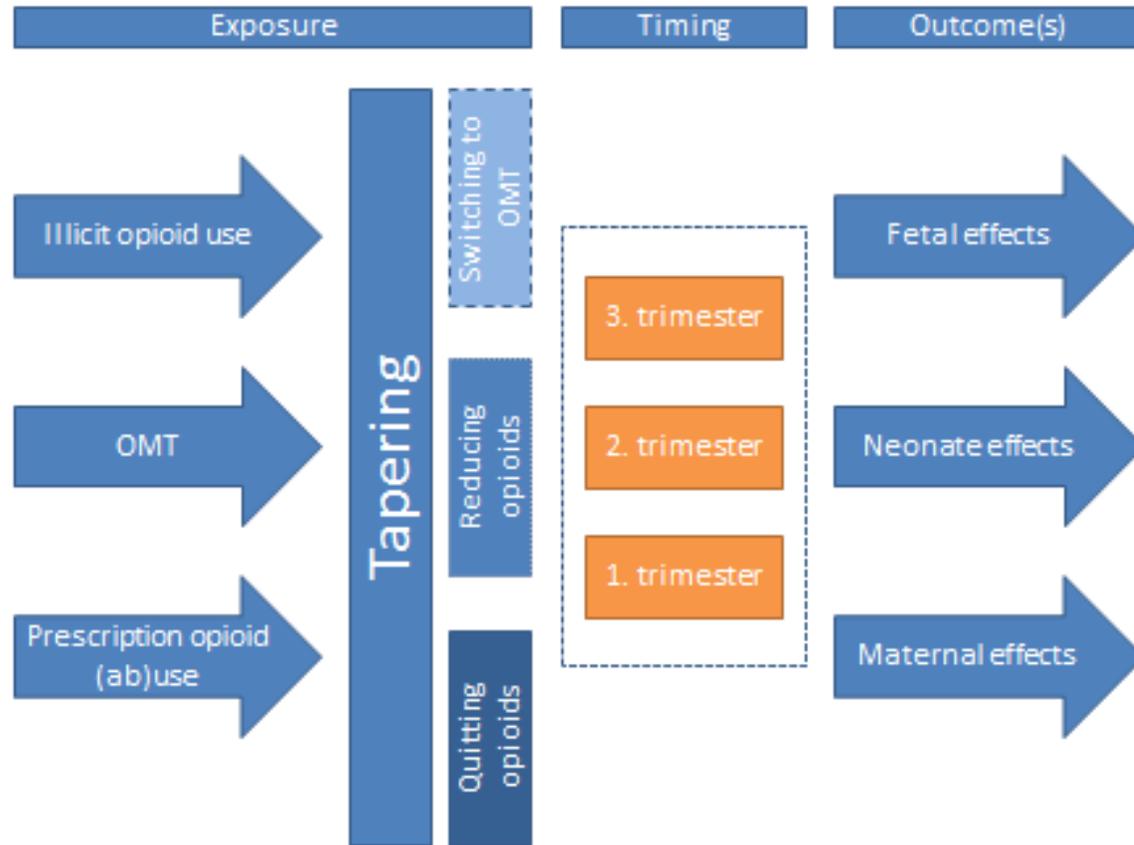


Figure 2. Flow chart of literature search

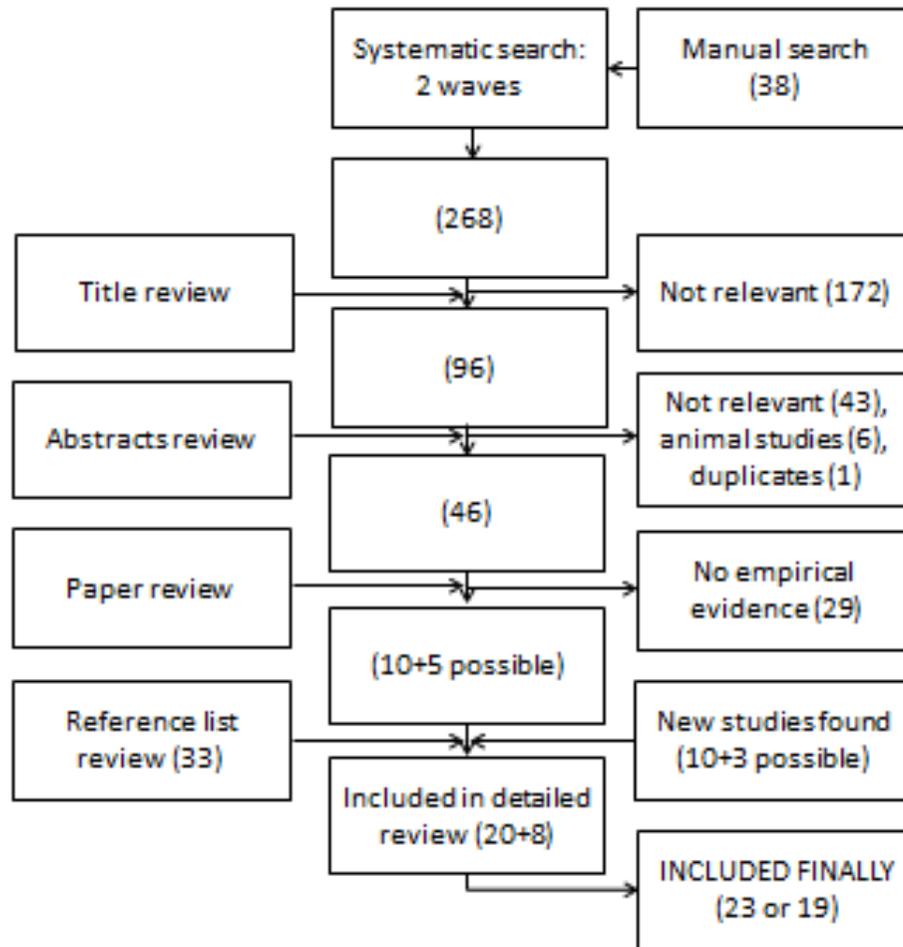
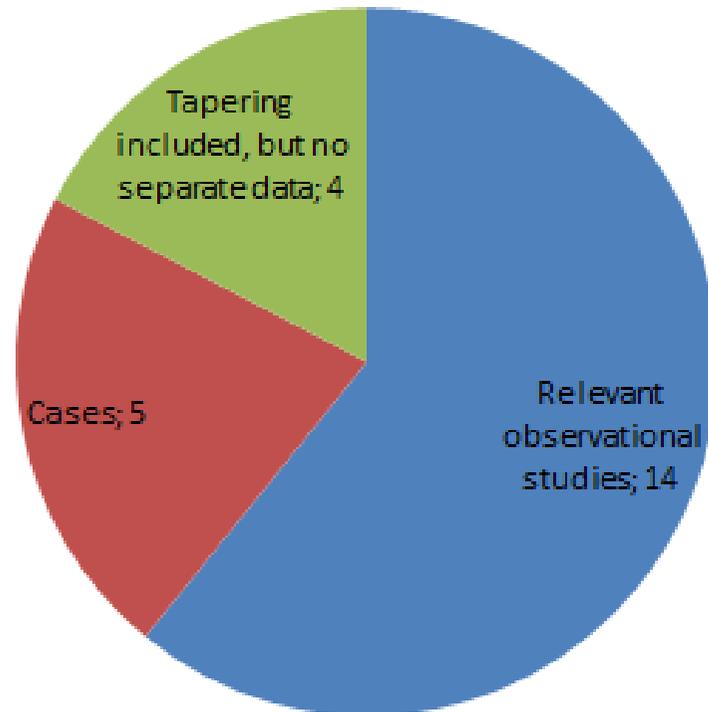


Figure 3. Last review of papers and their categorization



8.0 Appendix

8.1 Medline syntax

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> (the number of retrieved papers in parenthesis)

1. Opiate substitution treatment.mp. or exp Opiate Substitution Treatment/ (2384)
2. sorption detoxification.mp. or exp Sorption Detoxification/ (121364)
3. detoxification.mp. (28339)
4. opioid Maintenance Treatment.mp. (191)
5. medically assisted rehabilitation.mp. (0)
6. detox.mp. (315)
7. exp Methadone/ or methadone maintenance.mp. (13649)
8. drug rehabilitation.mp. (300)
9. exp Buprenorphine/ or buprenorphine.mp. (6751)
10. pregnant.mp. or exp Pregnant Women/ (167261)
11. exp Pregnancy/ or pregnancy.mp. (954828)
12. 10 or 11 (973717)
13. tapering.mp. (5633)
14. taper.mp. (4402)
15. withdraw.mp. (4225)
16. drug dose reduction.mp. (36)
17. drug withdrawal.mp. (3443)
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (167374)
19. 13 or 14 or 15 or 16 or 17 (17240)
20. 12 and 18 (3475)
21. 19 and 20 (35)

8.2 Embase syntax

Database: Embase <1996 to 2017 Week 04> (the number of retrieved papers in parenthesis)

1. opiate substitution treatment.mp. or exp opiate substitution treatment/ (1502)
2. methadone.mp. or exp methadone/ or exp methadone treatment/ (20832)
3. exp buprenorphine/ or buprenorphine.mp. (11902)
4. sorption detoxification.mp. or exp sorption detoxification/ (9)
5. opioid Maintenance Treatment.mp. (251)
6. medically assisted rehabilitation.mp. (2)
7. exp drug dependence treatment/ or drug rehabilitation.mp. (18984)
8. detox.mp. (383)
9. pregnancy.mp. or exp pregnancy/ (482488)
10. exp pregnant woman/ or pregnant.mp. (150803)
11. 9 or 10 (516756)
12. tapering.mp. (6678)
13. taper.mp. (4996)
14. withdraw.mp. (4767)

15. drug dose reduction.mp. or exp drug dose reduction/ (64946)
16. drug withdrawal.mp. or exp drug withdrawal/ (138645)
17. 12 or 13 or 14 or 15 or 16 (197575)
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (41005)
19. 11 and 18 (2081)
20. 17 and 19 (193)
21. limit 20 to exclude medline journals (25)

8.3 PsycINFO syntax

Database: PsycINFO <1806 to January Week 3 2017> (the number of retrieved papers in parenthesis)

1. exp METHADONE MAINTENANCE/ or exp METHADONE/ or methadone.mp. (6856)
2. buprenorphine.mp. or exp BUPRENORPHINE/ (2208)
3. exp Drug Rehabilitation/ (27875)
4. detoxification.mp. or exp DETOXIFICATION/ (3721)
5. opiate substitution treatment.mp. (54)
6. opioid Maintenance Treatment.mp. (121)
7. opiate replacement therapy.mp. (20)
8. 1 or 2 or 3 or 4 or 5 or 6 or 7 (34561)
9. pregnant.mp. (15705)
10. exp PREGNANCY/ or pregnancy.mp. (36155)
11. 9 or 10 (40589)
12. taper.mp. (502)
13. tapering.mp. (618)
14. withdraw.mp. (1929)
15. withdrawal.mp. or exp DRUG WITHDRAWAL/ (30469)
16. 12 or 13 or 14 or 15 (32659)
17. 8 and 11 (734)
18. 16 and 17 (112)
19. limit 18 to (danish or english or norwegian or swedish) (109)

8.4 Cinahl syntax

(The number of retrieved papers in parenthesis)

1. "opiate substitution treatment" (23)
2. (MH "Methadone") OR "methadone" (3,241)
3. (MH "Buprenorphine") OR "buprenorphine" (1,680)
4. (MH "Sorpton Detoxification+") (9,666)
5. "detoxification" (1,543)
6. opioid maintenance treatment (139)
7. medically assisted rehabilitation (569)
8. opiate replacement therapy (3)
9. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 (15,368)
10. (MH "Expectant Mothers") OR "pregnant" (19,064)
11. (MH "Pregnancy+") OR "pregnancy" (118,164)
12. S10 OR S11 (120,506)

13. S9 AND S12 (471)
14. Tapering (381)
15. Taper (430)
16. Withdraw (740)
17. "withdrawal" (8,345)
18. S14 OR S15 OR S16 OR S17 (9,603)
19. S13 AND S18 (70)
20. S13 AND S18 (21)

8.5 Cochrane summaries of knowledge

11 possible records were retrieved.

8.6 Second Medline syntax

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

1. pregnant.mp. or exp Pregnant Women/ (154544)
2. exp Pregnancy/ or Pregnancy.mp. (878757)
3. exp Sorption Detoxification/ (113703)
4. detoxification.mp. (25607)
5. detox.mp. (277)
6. tapering.mp. (5289)
7. taper.mp. (4219)
8. drug dose reduction.mp. (36)
9. drug withdrawal.mp. (3176)
10. exp Opiate Substitution Treatment/ (1820)
11. opioid Maintenance Treatment.mp. (173)
12. Methadone.mp. or exp Methadone/ (14996)
13. exp Buprenorphine/ or buprenorphine.mp. (5972)
14. opioid.mp. (88403)
15. opiate.mp. (19808)
16. 1 or 2 (897184)
17. 3 or 4 or 5 or 6 or 7 or 8 or 9 (150524)
18. 10 or 11 or 12 or 13 or 14 or 15 (106330)
19. 16 and 17 and 18 (102)

8.7 Titles and references of 63 papers redeemed relevant after reviewing abstracts (that were reviewed in full text)

Relevant?	Running ID number, title, author, journal, year	Type of paper
*	2. Caring for Pregnant Women with Opioid Use Disorder in the USA: Expanding and Improving Treatment. <u>Saia</u> KA et al., Current Obstetrics & Gynecology Reports, 2016.	Review
	5. Opioid detoxification during pregnancy: the door continues to open <u>Campbell</u> WA, American Journal of Obstetrics & Gynecology, 2016.	Editorial
E	6. Detoxification from opiate drugs during pregnancy. <u>Bell</u> J et al, American Journal of Obstetrics & Gynecology, 2016.	Observational study

E	8. Comparing methadone and buprenorphine maintenance with methadone-assisted withdrawal for the treatment of opioid dependence during pregnancy: maternal and neonatal outcomes. <u>Lund IO</u> et al, Substance Abuse and rehabilitation, 2012	Observational study
	12. Methadone versus buprenorphine for the treatment of opioid abuse in pregnancy: science and stigma. <u>Holbrook AM</u> . American Journal of Drug and Alcohol Abuse, 2015.	Commentary
E	13. Tapering from Methadone or Buprenorphine during Pregnancy: Maternal and Neonatal Outcomes in Norway 1996-2009. <u>Welle-Strand GK</u> et al., European Addiction Research, 2015.	Observational study
P	15. Narcotic tapering in pregnancy using long-acting morphine: an 18-month prospective cohort study in northwestern Ontario. <u>Dooley R</u> , Canadian Family Physician, 2015.	Observational study
P	18. Child neuroanatomical, neurocognitive, and visual acuity outcomes with maternal opioid and polysubstance detoxification. <u>Walhovd KB</u> et al, Pediatric Neurology, 2015.	Observational study
P	19. A woman's experience of tapering from buprenorphine during pregnancy. <u>Welle-Strand GK</u> et al, BMJ Case Reports, 2014.	Case
P	20. Incidence of narcotic abuse during pregnancy in northwestern Ontario: three-year prospective cohort study. Kelly J et al., Canadian Family Physician, 2014.	Observational study
	21. Identification and management of prescription drug abuse in pregnancy. <u>Worley J</u> . Journal of Perinatal & Neonatal Nursing, 2014.	Review = 186
E	22. The perinatal outcome of children born to women with substance dependence detoxified in residential treatment during pregnancy. <u>Haabrekke KJ</u> et al., Journal of Addictive Diseases, 2014.	Observational study
NR	23. Medication-Assisted Treatment With Methadone: Assessing the Evidence Fullerton CA, Psychiatric Services, 2014	Review
	24. The obstetric and neonatal impact of maternal opioid detoxification in pregnancy. <u>Terplan M</u> , American Journal of Obstetrics & Gynecology, 2014	Commentary
E	26. The obstetrical and neonatal impact of maternal opioid detoxification in pregnancy. <u>Stewart RD</u> et al., American Journal of Obstetrics & Gynecology, 2013.	Observational study
	27. Opioid addiction in pregnancy. <u>Shainker SA</u> et al., Obstetrical and Gynecological Survey, 2012	Review
	29. The treatment of alcohol and opioid dependence in pregnant women. <u>Heberlein A</u> et al., Current Opinion in Psychiatry, 2012.	Review
	38. Substance Use in Pregnancy <u>Wong S</u> et al., Journal of Obstetrics and Gynaecology Canada, 2011	Review
	47. Response to "Methadone Maintenance vs. Methadone Taper during Pregnancy" Paper. <u>Newman R</u> . American Journal on Addictions, 2009.	Commentary
E	50. Methadone maintenance vs. methadone taper during	Observational study

	pregnancy: maternal and neonatal outcomes. <u>Jones</u> HE et al., American Journal on Addiction, 2008.	
NR	57. Prescription opioid dependence and treatment with methadone in pregnancy. <u>Sander</u> SC et al., Journal of Opioid Management, 2005.	
	61. ["Is opiate detoxification unsafe in pregnancy?"]. <u>Newman</u> R, Journal of Substance Abuse Treatment, 2004	Commentary = 227
E	62. Is opiate detoxification unsafe in pregnancy? <u>Luty</u> J et al., Journal of Substance Abuse Treatment, 2003.	Observational study
NR	70. [Opiate dependent pregnant patients and mothers. What must be regarded in drug substitution and detoxification]. <u>Schwejda</u> C et al., MMW Fortschritte der Medizin, 2001.	Observational study
	74. Response to "Detoxification with Buprenorphine of a Pregnant Heroin Addict". <u>Welsh</u> CJ, American Journal on Addictions, 2000.	Commentary
P	75. Detoxification with buprenorphine of a pregnant heroin addict. <u>Annitto</u> WJ. American Journal on Addictions. 2000	Case
E	77. Opioid detoxification in pregnancy. <u>Dashe</u> JS et al., Obstetrics and Gynecology 1998.	Observational study
P	79. Substance abuse treatment for pregnant women: a window of opportunity? <u>Daley</u> M et al., Addictive Behaviors, 1998.	Observational study
	88. Detoxification considerations in the medical management of substance abuse in pregnancy. M. H. <u>Allen</u> , Bull N Y Acad Med. 1991	Review
E	89. Infrequent neonatal opiate withdrawal following maternal methadone detoxification during pregnancy. <u>Maas</u> U et al., J Perinatal Medicine, 1990.	Observational study
E	98. Drug addiction in pregnancy and the neonate. <u>Blinick</u> G et al., American Journal of Obstetrics and Gynecology. 1976	Commentary
E	99. Fetal stress from methadone withdrawal. <u>Zuspan</u> FP et al, American Journal of Obstetrics and Gynecology. 1975	Case
E	101. Pregnancy in narcotics addicts treated by medical withdrawal. The methadone detoxification program. <u>Blinick</u> G et al., American Journal of Obstetrics and Gynecology. 1969.	Observational study
	102. Intrauterine abstinence syndrome (IAS) during buprenorphine inductions and methadone tapers: can we assure the safety of the fetus? <u>McCarthy</u> JJ. J Matern Fetal Neonatal Med. 2012	Review
	118. Medication assisted treatment discontinuation in pregnant and postpartum women with opioid use disorder. <u>Wilder</u> C et al., Drug Alcohol Depend. 2015	Review
P	129. Randomized controlled study transitioning opioid-dependent pregnant women from short-acting morphine to buprenorphine or methadone. <u>Jones</u> HE et al., Drug Alcohol Depend. 2005	Observational study
NR	131. Buprenorphine and methadone in pregnancy: effects on the mother and fetus and neonate. <u>Gordon</u> AL. (doctoral thesis) University of Adelaide, School of Medical Sciences, Discipline of Pharmacology, 2006.	Not tapering
E	142. Scientific evidence and practical experience with	Observational study

	methadone-assisted withdrawal of heroin-dependent pregnant patients. <u>Jones H</u> . Heroin Addiction and Related Clinical Problems, 2008	
NR	152. Experience with buprenorphine induction and subsequent dose reduction as compared to treatment with L-methadone in pregnant opiate addicts. <u>Siedentop JP</u> et al., Geburtshilfe und	Observational study
NR	155. Use of buprenorphine during pregnancy. M <u>Reisinger</u> , Research and Clinical forums, 1997	
E	161. Opiate Detoxification of Pregnant Women Using Clonidine: An Observational Cohort Study. <u>LePreau FJ</u> et al., Journal of Women's Health. 1995.	Observational study
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*E: study includes empirical data that that can be useful in study, P: study includes empirical data that that potentially can be useful in study, NR: not relevant for study