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Intrauterine abstinence syndrome (IAS) during buprenorphine inductions and methadone tapers: can we assure the safety of the fetus?

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LETTER TO THE EDITOR

Intrauterine abstinence syndrome (IAS) during buprenorphine inductions and methadone tapers: can we assure the safety of the fetus?

McCarthy [1] raised some important concerns regarding the potential deleterious impact on fetal development of in utero exposure to opioid-agonist medications. The paper has two disparate foci: (1) Reviewing studies regarding fetal opioid withdrawal; and (2) Critiquing the Mother Study [2].

Intrauterine abstinence syndrome: awaiting definition

McCarthy's article posits the existence of an "Intrauterine abstinence syndrome (IAS)" while failing to define it. In the absence of supporting data, identifying a syndrome based on the suspicion of its existence as a medical entity is neither relevant nor clinically useful. The concern that the fetus may experience opioid withdrawal under certain conditions is valid; however, it is premature and misleading to offer the existence of a newly-named syndrome – without any attempt to define the syndrome itself, including its recognizable signs and clinical features. The argument that "We have an acronym for the neonatal abstinence syndrome (NAS), but none for the IAS" misleadingly implies that IAS has been defined, and data exist to support its utility in understanding fetal health and well-being.

The primary justification for prescribing agonist treatment for opioid dependence during pregnancy is to stabilize the intrauterine environment to protect the fetus from repeated episodes of maternal withdrawal [3]. However, the extent to which maternal opioid withdrawal has adverse consequences on the fetus, child, and adult remains to be fully elucidated, as do other potentiating or protective maternal and/or fetal factors that might operate during maternal withdrawal. The primary questions – none of which McCarthy's article raised – are: What is the relationship between severity of maternal withdrawal and fetal physiology/development, and if fetal effects exist, which are transitory, which are enduring, which are minor, which are major, and how such effects adversely affect fetal development. Controlled research is certainly needed to examine these relationships, with a clear understanding of the ethical issues involved. Such research would then make it possible to determine whether an IAS exists, and examine its short- and long-term effects.

Selective literature review and presentation

Possible fetal withdrawal resulting from buprenorphine induction is extensively discussed in the absence of any supporting data. Omitting mentions of animal methodological details incorrectly implies that all referenced studies speak directly to potential maternal buprenorphine induction harms. Umans and Szeto [4] infused morphine for 2–6 hours into fetal lambs, then administered naloxone once. Lichtblau and Sparber [5] maintained their rat dams on LAAM (*l*-α-acetylmethadol), then administered naloxone on day 14 of gestation through term. Schrott et al. [6] used NLAAM (*N*-desmethyl-*l*-α-noracetylmethadol) to induce in ovo opioid dependence in chick embryos, then precipitated withdrawal with naloxone in late-stage embryogenesis. The results of this diverse animal withdrawal research fail to address the impact of mild-moderate withdrawal that a human fetus might experience in a typical maternal buprenorphine induction.

Furthermore, McCarthy's article ignores data arguing against his conclusions. For example, Jansson et al. [7] found that early (24 and 28 weeks) and late (32 and 36 weeks) gestation fetuses had more optimal functioning in cardiac and movement parameters, respectively, in the buprenorphine- than in the methadone-exposed condition. A larger sample [8] of 81 MOTHER fetuses at 31–33 weeks gestational age indicated, among other findings, that there was a significantly higher frequency of non-reactive non-stress test in fetuses in the methadone *v*. the buprenorphine condition. Buprenorphine produced less suppression of fetal heart rate, fetal heart rate reactivity, and a higher biophysical profile score after medication dosing, suggesting that fetal risk is no greater for buprenorphine than for methadone. Both studies included buprenorphine-induction-exposed fetuses. Not only did the buprenorphine-exposed fetuses display more optimal functioning, but the resultant infants had less severe NAS relative to their methadone-exposed counterparts. Moreover, methadone itself has also been demonstrated to negatively impact fetal neurobehaviors in the absence of significant maternal physiological changes [9]. Although hardly definitive, these results suggest the answers are "Yes" and "No", respectively, to two questions posed in McCarthy's article: "This raises the important questions of whether the risks of induction on buprenorphine have counterbalancing benefits, or whether benefits in reduced NAS measures come as a result of inflicting an unacceptable stress on both mother and fetus."

Moreover, McCarthy's article unjustifiably warned that "... on a cautionary note relative to buprenorphine's putative reduced risks of NAS severity, a national prospective Norwegian study found more treatable NAS in buprenorphine-exposed neonates (67%) than those exposed to methadone (58%)". This study [10] clearly states: "There were no statistically significant differences between the 2 groups for the occurrence ($p = 0.73$) and duration of NAS ($p = 0.64$)." Such a finding, in a relatively small sample of 38 women, only 12 of whom received buprenorphine, hardly raises a caution about MOTHER's conclusions regarding buprenorphine. The failure to accurately describe the outcome of this study, coupled with the failure to cite other published studies reporting superior NAS outcome in buprenorphine- *v*. methadone-exposed infants [11–15], suggests poor scholarship or a bias against buprenorphine.

Finally, McCarthy's article ignored the myriad other effects that may compromise development in opioid-exposed fetuses, including maternal licit and illicit drug use, notably, alcohol, nicotine, and psychotropic medications, inadequate nutrition,

infections, depression, untreated pain, physical violence exposure and, sexual victimization [2,3,16]. Drug use rarely occurs in the absence of these (and other) confounding bio-psycho-social influences. Indeed, these factors may account for a sizeable proportion of the incidence of fetal demise and compromised fetal development in fetuses exposed to either buprenorphine or methadone. Thus, the relative risks and benefits of any medication, including buprenorphine, to treat opioid dependence during pregnancy must be viewed in the context of these dynamic complicating factors. Arguing that agonist medication selection should be singularly based on its relative impact on the potential for fetal opioid withdrawal during induction ignores the everyday difficulties many opioid-dependent women face, and their need for comprehensive care in order to make substantive and enduring changes in their lives.

MOTHER study: need for clarification

There are numerous concerns we have regarding representations of the MOTHER study [2] in McCarthy's article. For example, McCarthy's article incorrectly stated that in MOTHER, "methadone had better retention" than did buprenorphine. The hypothesis of a difference between the buprenorphine and methadone conditions in retention was directly tested in MOTHER, and failed to be rejected.

Moreover, McCarthy's article devotes an entire paragraph to why the MOTHER buprenorphine sample was more likely to be "dissatisfied" – which he misstates as "rejected" – with their medication than was the methadone sample. The conclusion blames the medical staff for a non-significant difference in retention between the two medications: "Making sure a pregnant woman is in hard opiate withdrawal would not be emotionally easy for any medical staff. So inducing on buprenorphine before such hard withdrawal occurs is understandable. This makes precipitated withdrawal the far more likely outcome, and helps explain why buprenorphine retention was problematic." MOTHER had standardized double-blinded induction procedures. Arguing that staff failed to follow induction procedures, and instead responded to personal emotions to administer medications and thereby precipitate withdrawal, is pure conjecture. Rather, a different induction protocol from that used in MOTHER might result in more patient satisfaction, as Jones et al. [2] noted. Induction protocols merit future research instead of a simple dismissal of buprenorphine based on speculation. A clear distinction is needed between the need for effective induction protocols and an evaluation of buprenorphine's relative effectiveness.

Treating the mother-fetus dyad or treating fetus versus mother?

The assumptive bias of McCarthy's article is found in its conclusions: "But the primary goal of the obstetrician and addiction physician must be fetal safety, especially when neonatal symptoms are treatable and fetal symptoms can go undetected. At this time, methadone maintenance remains the best way to protect the fetus." This statement implicitly pits the fetus against the mother, rather than conceptualizing the patient as the mother-fetus dyad. The article is also silent on the ethical issues surrounding decision-making for mother and fetus, and the concept of the fetus as patient [17–20]. Critical literature regarding how best to handle the issues health care professionals face in weighing the impact of treatment on mother, fetus, and child, in both research and clinical practice, is not mentioned. Although support for a position that the fetus is (or is not) a patient separate from the mother is far from uniform, McCullough and Chervenak [21] cogently sum up the issue: "The pregnant and fetal patients are not separate patients, because beneficence-based obligations to the fetal patient *and* beneficence-based obligations to the pregnant women must *always* be taken into account in clinical ethical obstetric judgment".

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Author's response:

The letter from the MOTHER study group is important for a dialogue concerning fetal withdrawal in opiate addiction treatment, a neglected area of research. The authors state that: "The concern that the fetus may experience opioid withdrawal under certain circumstances is valid". And they concede that a buprenorphine induction exposes the fetus to "mild-moderate withdrawal". I cited 2 studies (Zuspan 1975, Rementaria 1973) that demonstrated that fetal withdrawal can also be fatal.

The authors do not agree with the use of the term Intrauterine Abstinence Syndrome (IAS) to describe fetal opiate withdrawal. This lack of agreement is not based in the facts that can be identified. A syndrome is an association of several clinically recognizable signs or symptoms that occur together, so that the presence of one alerts the physician to the possible presence of others. If a mother is in withdrawal, then I have cited the evidence that we can infer that the fetus is in withdrawal and can suffer a hyper-motoric, excessive catacholaminergic state, associated with fetal hypoxia and meconium staining [1,2]. I documented these characteristics of IAS from clinical studies in the pre-methadone era, contemporary authoritative textbooks, and animal models. To say my review lacked "supporting data" completely ignores this evidence. Furthermore, since deliberately putting a pregnant mother and fetus into withdrawal in a research study is an ethically questionable practice, animal models are critical and they clearly document a syndrome. The term IAS is scientifically accurate and some signs are documentable (see below).

Whatever we call it, fetal withdrawal occurs, and failure to give it a name may encourage the mistaken notion that it does not occur or is not clinically important. There was no mention of buprenorphine's antagonist effects or any mention of fetal withdrawal risks during buprenorphine induction in the MOTHER study publication [3]. In fact the MOTHER study

did not study fetal response to the prolonged randomization/induction process with its requirement for multiple episodes of maternal withdrawal, especially in the case of methadone transitions. And a safe and practical induction protocol was never established.

I am familiar with Dr. Jansson's important work. It was beyond the scope of my focused review of precipitated withdrawal. However, the study cited is important and has unanticipated implications [4]. Dr. Jansson studied mothers on single doses of methadone, a regimen that does not promote stability because of the accelerated metabolism of methadone in pregnancy [5]. Multiple dose regimens, at least BID, are necessary to prevent maternal withdrawal. In a previous study Dr. Jansson and colleagues documented improvement in fetal cardiac parameters on a BID methadone regimen compared to QD dosing [6]. This suggests that what they hypothesized as a toxic effect of methadone on cardiac function was, at least in part, effects of a dose regimen that is un-physiologic for the fetus. They quoted Swift et al that split doses "result in fewer withdrawal symptoms in the *mother and infant* [6]"(italics mine). What they may have documented is a cardiac feature of IAS: effects of fetal withdrawal during single dose methadone regimens that expose the fetus to high peak levels and rapid declines.

Dombrinski, a clinician experienced in using split doses of methadone, has theorized that when adequate split doses are used, "the fetus does not develop an adverse reaction to periodic withdrawal in the womb", reducing signs and symptoms of NAS [7]. There is preliminary evidence that repeated opiate withdrawal sensitizes the fetus and may increase risks of NAS [8].

Further documentation of IAS comes from an ultrasound study of single and split doses by Whittmann and Segal [7]. They documented highly significant fetal behavioral abnormalities on single dose regimens, including percent of time spent breathing, number of rotational body movements, and longest period of fetal activity prior to the AM dose. These changes normalized on a BID regimen. Ultrasound was able to document the hyper-motoric aspects of IAS. The MOTHER study used single doses of methadone, a variable confounding conclusions about NAS severity and cardiac safety in the methadone arm.

In quoting the Norwegian study, I did not fail to "accurately describe the outcome". I deliberately stated the percent of treatable NAS because the buprenorphine group had a very high incidence (68%). This variability is very characteristic of the NAS literature for both methadone and buprenorphine. That was my point. The methadone and buprenorphine groups were statistically similar in incidence of overall rates of NAS needing treatment and did not totally support the conclusions of the MOTHER study.

NAS is a quagmire of research contradictions. A review of 37 studies on the relationship of methadone dose to NAS, by Cleary et al. [10], found that 18 refuted the conclusions of the other 19. They found that rates of treatable NAS in methadone-exposed neonates ranged from 13–94%, for exactly the reasons the MOTHER group states: too many variables to control for. As has been previously postulated (5,6,7), some of the confusion in the methadone dose/NAS literature may occur because high doses given as a single dose may still expose the fetus to daily withdrawal episodes.

Another potentially significant uncontrolled variable occurred in the MOTHER study, in spite of the extraordinary lengths the researchers went to control variables related to NAS. The study used an average methadone dose of only 78 mg/day, which seems quite low for a pregnant population dosed with a goal of eliminating all symptoms of maternal withdrawal. In an on-going prospective study in our pregnancy program ($N = 37$ to date), the average methadone dose at delivery is 135 mg/day, given in divided doses (BID-QID). Serial trough serum levels average 250 ng, documenting methadone hyper-metabolism. The incidence of NAS treatment to date in our study is 27%, about half of the rate found in the MOTHER study for either methadone or buprenorphine, demonstrating again the variability of NAS. It also raises the theoretical possibility that eliminating problematic peaks and troughs may reduce fetal sensitization and reduce NAS severity.

The authors state that the hypothesis regarding a difference in methadone and buprenorphine retention in the MOTHER study "failed to be rejected". This confusing statement stands in contrast to their published conclusion that "results must be considered in light of markedly different rates of attrition, which were largely due to greater patient dissatisfaction with buprenorphine than with methadone [1]". Greater attrition vs. poorer retention seems a point of obfuscation only.

Opinions were expressed on how emotionally difficult it can be for a compassionate physician to watch a pregnant mother endure acute withdrawal until they are sick enough to be given buprenorphine. As a physician with a specialty in psychiatry, these statements were calling attention to the fact that there are important human emotions that cannot be ignored. The authors misinterpreted my statements which were not to criticize the medical judgment of MOTHER study staff but to emphasize that there is the art of medicine as well as the science that must be considered in such situations. My question to the MOTHER Study investigators about how sick pregnant women need to be before buprenorphine administration remains unanswered.

For 40 years the goal of agonist therapy in pregnant women has been to keep mother and fetus out of withdrawal, as these authors correctly state. However, to accept "mild-moderate (fetal) withdrawal" during buprenorphine induction as an acceptable risk is a new and unproven paradigm. I do not believe we have the research evidence yet to say this risk is acceptable, especially in community use where none of the fetal safeguards used in the MOTHER study are in place. That is not a bias but a medical risk/benefit analysis that favors methadone. Inflicting stress on the developing fetus, as opiate withdrawal does, has potential long-term implications, which I discussed, that would seem to advise caution. I hope this excellent research collaborative will give more attention to the issue of fetal withdrawal. If it does, my use of the term IAS will certainly have accomplished its goal.

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