

So why are we talking about this? Why would anybody think that labor pain has anything to do with depression in the perinatal period? So I'm glad you asked. In the chronic pain world there is certainly a known and well established association between pain and depression, so that frequently these are common bedfellows. If you treat one of these - they are comorbid conditions, if you treat pain in a chronic pain patient who is also depressed frequently their depression gets better. And vice-versa, if you treat their depression frequently their pain gets better too. Mechanistically speaking we know that this is potentially related to areas in the brain that are activated in both pain and depression. In particular here on these images you are seeing overlapping areas in depression and in acute pain in the anterior cingulate gyrus which are activated in both conditions and it's involved in both identification recognition and evaluation of pain and as well as affective components of depression.

But what we really don't know is how this relationship plays out in the perinatal period. So what impact might there be on acute pain during the labor and delivery period which for many women can go on for hours and their risk for mood disorders in the postpartum period. There is some compelling research that I'll present later on that suggest that there may be a relationship here that's worth investigating further.

Furthermore we know that maternal - the consequences of maternal depression impact more than just the mother herself, so yes she can be very down in the perinatal period which impairs her ability to care for herself but it also impairs her ability to care for her baby, and that can have negative impact on the baby. So that this impaired maternal infant attachment can lead to

impaired infants and child development and this affect can actually last well in to the adolescent period.

So this was a very well known and quoted study from I believe Scandinavia that was a prospective longitudinal study over 16 years, some very, very patient investigators who followed women who were depressed and their children and also followed when they were not depressed and their children and found that the impact of the mother's depression lasted well past adolescence into - well into adolescence, into 16 years. So that children of index mothers were also, were themselves at elevated risk for depression at 16 years with an odds ratio of almost 5. And other predictors of this are well known and recognized including lower childhood resilience which may be related to an impaired mother, and also the insecure infant attachment which we talked about.

So for the rest of this presentation what I'd like to do is basically provide for you a historical and a social context for modern labor analgesia. We'll talk about the pathophysiology of labor pain. We'll also talk about the neurophysiologic basis of pain and depression. And then I'm going to briefly touch on some current research on pain and postpartum mood and function.

So labor analgesia is actually pretty relatively new in the context of history, so it was first described by James Young Simpson who was an obstetrician in the 1820s and '30s who began writing case reports on accounts of how he was offering ether to women during labor. He was a very unpopular obstetrician, nobody really accepted what he was talking about but he persisted

in his viewpoints that pain really had no role in labor and delivery and he wanted to do what he could to make it better. So his viewpoints were really not well adopted but it wasn't until John Snow came around who was another obstetrician who is probably best known for his epidemiological work in the area of cholera. He was a key player in the elimination or the eradication of cholera.

He was actually the obstetrician for Queen Victoria during her birth, her delivery of Prince Leopold. And she actually demanded some form of analgesia. She called pregnancy a wretched state, she was probably a revolutionary in this regard for her time. And John Snow provided chloroform to her and the experience was overwhelmingly positive. He wrote about it in his 1830 something treatise, Chloroform and Other Anesthetics. Queen Victoria described it as that blessed chloroform, soothing, quieting and delightfully beyond measure. And John Snow said that she was very cheerful and well, expressing herself, much gratified with the effect of the drug.

Despite the use of chloroform in this very prominent public figure it didn't take long before there was a backlash from the medical community. This was a letter that was penned to The Lancet in 1834 and endorsed by 12 to 16 obstetricians at the time who definitely condemned its use, they came out very strongly against it. They said that Her Majesty was placed under the influence of chloroform, we know unquestionably that chloroform has been linked to death. In no cases could it be justifiable to administer chloroform in a perfectly ordinary labor. And they went on

to say that they couldn't imagine having to be the physician taking care of the Queen and having to give her something like this.

So despite the condemnation from the medical community really it was patients who drove the popularization of labor analgesia. So these were suffragettes and it really was around this time the suffragette movement when women were demanding that pain be relieved during labor. They saw no point to the suffering and despite the outcries from the medical community they still demanded its use. It kind of sounds like history repeating all over itself these days in terms of patients driving medical care.

But nevertheless despite that public popularization the dichotomy in this debate persisted in the medical community. On the left this is James Meigs, he was an obstetrician in 1936, he was the most outspoken critic of the use of labor analgesia and he basically his stance was that labor pain has a purpose, uterine pain is inseparable from contractions. And all the while you know James Young Simpson persisted in his viewpoints very publically saying things like all pain is without physiologic value.

So what's striking to me about this whole thing is that this dichotomy about the nature and significance of labor pain has persisted almost 200 years after these debates seemed to have begun. So that these days it seems like the modern woman who is pregnant seems to belong to one of two camps. One camp on the left is a woman who wants to embrace the entire birth experience, pain included and does everything in her capability to enroll friends and other people

in her social support network to experience this to its fullest - to her fullest ability. And in the other camp is another group of women who seem to embrace any medication at all whatsoever during labor or at least don't mind it. Part of the reason why I think this debate continues to persist is because pain in general is an inherently subjective experience. The IASP, which is the International Association for the Study of Pain, has defined pain as an unpleasant sensory or emotional experience associated with actual or potential tissue damage, there doesn't even need to be real tissue damage, or described in terms of such damage. And this really highlights central tenet in pain medicine in general, and that is that pain without cognition or pain, you know painful stimulus without the ability to cognitively appraise that situation is simply a phenomenon called nociception.

In anesthesia we see this every day in patients that we render unconscious under general anesthesia and whom we actually can still see physiologic responses to surgical stimulus. So we'll still see an elevation in heart rate, we might still see elevations in blood pressure, but they are unconscious so without the ability to process that we can only describe as a nociceptive sensation or a phenomenon.

So the pathophysiology of labor pain is such that in the first stage of labor, in the first stage of labor which is associated or basically defined as the onset of labor whenever or whatever that might be up until 10 cm or fully cervical dilated we have a visceral pain component that is transmitted via sympathetic nerves and inserts into T10 through L1. In the second stage of labor we have transmission of pain fibers that are somatic in nature so that's pain that's basically

associated with skin and some tissue stretch transmitted through the pudendal nerves into S2 through S4 areas. And what this means is that we actually have pretty focused targets that we can use to control pain should a woman request some kind of intervention for analgesia. That includes things like segmental epidural blocks, lumbar sympathetic blocks and paracervical blocks which can be assistive in the first stage of labor types of pain. And second stage of labor pain can be adequately addressed with caudal blocks, paracervical blocks, pudendal blocks or sacral nerve blocks.

In modern anesthesia we really don't see any of these blocks in practice, but we are able to offer most women that takes care of both first and second stage of labor is basically a lower lumbar epidural technique in which we basically introduce an epidural catheter to the lower lumbar areas and through the spread of volume of medication we can take care of T10 through even the sacral dermatomes in order to cover all of the painful sensations of labor.

There is also a known physiologic basis for pain during labor. Afferent terminal components we know are able to be modified in their response to various sensations so that during cervical widening or the very first stages of labor there is an activation of various terminals by bradykinin, heat, PGE2, TNF α , IL-1 β and nerve growth factor. And what we know is that through the progressive stimulation of these terminals we have an increase in sensitization which means that over time pain becomes - the sensation of pain becomes increased and amplified in terms of its sensation and intensity. So in other words, pain becomes, labor pain becomes more painful over time because of the persistent activation of these terminals.

You can imagine that there is tremendous interindividual variability here because there is differential genetic components and interindividual components that influence the expression of these receptors, so that explains partly why there is such a wide and varied response or wide and varied patterns to both cervical dilation and the process of labor itself as well as the pain of labor. Not only are these factors associated with pain but they are also associated with depression, so there does seem to be some overlap between these factors and depression and pain. So TNF α and IL-1 β for example are known to also be associated with depression in addition to all of these other mediators so that our studies so far would be biochemical studies have basically shown that genetic variance in the expression of these factors, all of which are listed in red, are associated with variable expressions of depression in the perinatal period, so increased or decreased susceptibility to depression in the perinatal period.

There are other biological explanations for perinatal depression, the most popular of which is the idea of perinatal hormonal shifts. So throughout pregnancy you have general increases in levels, circulating levels of progesterone and estrogen and during the delivery period you see a rapid withdrawal of these hormones. So this is one study that basically looked at predelivery and postdelivery progesterone levels between women who are depressed and women who are not depressed. And not only do we see significant differences in predelivery progesterone concentrations in that depressed women were more likely to exhibit or have higher concentrations of circulating predelivery progesterone but they are also going to have lower circulating levels of postdelivery progesterone. And this is not pictured here but what this

essentially points to is that the rate of decline of these circulating hormones seems to be associated with the onset of these mood disorders in the perinatal period.

Another hormone that's been identified is allopregnanolone and this is a derivative or a metabolite of progesterone. And what's been seen in some studies in this area is that - and allopregnanolone by the way is a GABAergic agonist so we know that that is - so we know that that is associated with mood and an excitatory state in general. So what they've seen in these studies is that women who are blue or dysthymic, depressed but to a moderate or milder degree. These women are more likely to have lower levels of circulating allopregnanolone than their euthymic counterparts. In this particular study they did not see any difference between these two populations in terms of circulating levels of progesterone but clearly there is some kind of trend and probably this particular this particular study was underpowered for that association.

The other association that's important to note is that in euthymic or normal mooded women the relationship between progesterone and allopregnanolone seems to be normal, meaning the Pearson correlation between the two of them is significant and normal; but there appears to be some kind of an issue between - an issue between progesterone and allopregnanolone's relationship in patients who are dysthymic. So this points to not only a problem with absolute circulating levels but also the metabolism of these hormones in the perinatal period and those things may also be influential in the expression of depression in the perinatal period.

So that's all well and good but what is the impact of labor pain on depression? I think in order to begin answering this question we have to ask ourselves another more basic question which is that is labor pain physiologically functional at all? There are two parts of that argument that are normally made. One of them is that pain increases plasma catecholamines which has an effect on the progress of labor itself, and that pain enhances Ferguson's reflex which also influences labor. So pain induces a catecholamine surge. You can imagine you are in a lot of pain, you have got a lot of circulating epinephrine and norepinephrine going around. And we know that these hormones, in particular epinephrine, are key in the regulation of normal rhythmic uterine contractions. The normal levels of circulating epinephrine and norepinephrine also are helpful in maintaining a normal tone of the uterus because without these hormones basically the uterus would be constitutionally tonic and then you'd have problems with placental perfusion and perfusion to the baby.

We have some indirect evidence of this association in that we know that numerous observational studies have shown that when you introduce labor epidurally, and I'll use an example to a woman who is having dysfunctional labor or who is having irregular uterine contractions or contractions of a pattern that can't be predicted or cervical dilation just going on forever once you introduce some kind of pain relief epidurally analgesia it's been demonstrated numerous times that that actually can normalize the labor curve for those women. That is not a consistent demonstration however because there is certainly more commonly something we see almost on a daily basis any time we introduce labor epidurally analgesia in a rapid fashion to somebody who let's say is going through a lot of pain, so those women who are having a lot of pain arguably may have

elevated levels of circulating catecholamines, epinephrine and norepinephrine. And when you rapidly withdraw that from circulation we see an abnormal pattern of contractions, we see hypertonus or uterine tachysystole is the more correct term in which you are seeing more frequent contractions perhaps even stronger contractions and you even begin to see impairment in uterine perfusion because the fetal heart rate can be changed in that sense. Normally that's all easily treatable by the way. But there is again some indirect evidence of pain's role in labor in general.

The other way that pain might influence labor is through Ferguson's reflex. Now what this is is basically a positive feedback loop for oxytocin. So you have the onset of labor and that is mediated in some ways by oxytocin, and through pain basically there is a positive feedback loop so you get more oxytocin, you get more contractions and there is also an increase in receptor reactivity to that. So this is the theory behind that. Now the role of pain in this actually and the role of analgesia is less well established. There are some studies that show that analgesia induces reductions in plasma oxytocin concentrations, and there are some studies that show it makes no difference.

So here is one study that looked at intrathecal sufentanil on plasma oxytocin concentrations and found that there is actually a significant decline in circulating oxytocin concentrations among women who receive intrathecal sufentanil. On the other hand here is another study that looked at oxytocin concentration over time after the introduction of epidural analgesia and found there was pretty much no change among these women.

Also without labor pain we know that labor is slower. Now the clinical, the statistical significance of this is pretty recognized but the clinical significance of this is up for debate. So here was a randomized controlled trial in 2000 nulliparas women who either got an epidural or intravenous meperidine and it was an intent to treat analysis to show that basically both stages of labor, first and second stage of labor, do have significant reductions in time, meaning it was longer, meaning the labor was longer in patients who got epidural analgesia. But the you know clinical significance of the first stage of labor being 7 versus 8 may be debatable. On the other hand, the second stage of labor there certainly was a statistically significant difference between these two groups; but with a difference of 13 minutes you can be a judge of whether or not that's clinically significant.

On the other hand the findings are certainly reproducible, this was another study in nulliparas women that looked at the second stage of labor and certainly there is a significant difference between the two groups of analgesia epidural or none in terms of the length of labor by almost half an hour of duration. And again you be the judge about whether or not that is clinically significant.

So the other end of this coin or the argument is that labor pain is not functional. And this is primarily a medical anthropological viewpoint. There is prevailing theory called the obstetrical dilemma which basically holds that we as a human species evolved to favor narrow pelvises with narrow pelvic outlets because this makes us more efficient at walking and running. But also we

as a human species evolved to favor larger brains. And these two events seem to be a little bit mutually exclusive, so that compared to other normal or to compared to other nonhuman primates we actually deliver our children at an earlier stage of development which is partially why you see the disproportion in head to body ratios. And also our labors are more painful. So the idea here is that pain as a function of labor really has nothing to do with anything physiological and is just a terrible byproduct of an imperfect evolution.

Marlene Zuk who is an evolutionary biologist said it best when she said you can't give birth to large brained infants and also walk on 2 legs trouble-free. So you know the bottom line here is when compared to other nonhuman primates human birth is unique in the sense that ours is painful and theirs is not.

There are negative effects of perinatal pain and we'll talk about depression in a little bit, but also traumatogenesis is a key component here. So there is some interesting recent work that came out of China a couple of years ago that looked at women who either received an epidural for labor and who chose not to. It was a prospective observational study that was unique in that it was conducted at a time when this particular hospital was just beginning to use epidural analgesia more often than they were before, so that potentially minimized the risk of bias in selection.

What they did find very interestingly was that among women who chose to use epidural analgesia their risk for depression was lower than women who did not. There were a couple of

limitations with the study: one, it was observational in nature so there was no way and still is no way to really demonstrate causation; but also because they were not able to account for many of the other factors that influence risk for depression it's hard to know whether or not the epidural itself was effective and if there was something about pain control that alleviated the risk for depression or if it was the choice and you know the characteristics of the mother who made the decision to use epidural analgesia that drove that decreased risk for depression. So a woman who felt more empowered in this particular culture to ask for an epidural for pain relief may have been at reduced risk to you know exhibit depression in the postpartum period. So again that could not be addressed in this particular study.

But it does seem to be corroborated by some evidence in the pain literature. This was a study done by Jim Eisenach in 2008 and he found that acute pain in the postpartum period was associated both with chronic pain and depression scores at 8 weeks, so that for every point increase in acute pain in the postdelivery period there was a commensurate 8.3% increase in depression scores in the postpartum period, and also an increase in the odds of chronic pain or 8 week pain afterward. This relationship actually interestingly persisted regardless of mode of delivery. So Cesarean delivery or not had no relationship at all to both the acute pain scores and also the risk for depression at 8 weeks.

So another study has actually looked at pain relief by epidural or pericervical blocks or nitrous oxide or acupuncture and compared it to no analgesia at all. And this particular group from France I believe found that women who used epidural or had an epidural block or a paracervical

block for delivery had reduced risk for depression symptoms, or depressive scores in the immediate postpartum period compared to women who had no analgesia. But surprisingly and maybe even more importantly, at about 4 months this particular relationship did not hold anymore.

So in an attempt to address some of those study limitations and also to ask the question whether or not pain is what's mediating this relationship our group has looked at pain during labor and risk for depressive symptoms in the postpartum period. So what we did was we looked at a cohort of about 200 women who received epidural analgesia at Magee Women's Hospital and who had pain scores recorded during their labor. And we calculated a percent improvement in pain which is essentially the difference between the pain they had before they had epidural analgesia and the pain that was experienced after the implementation of labor epidural analgesia. And what we found is a significant negative relationship between these two components such that a woman who is experiencing greater improvements in pain after epidural analgesia was more likely to have reduced postpartum depression symptoms at 6 weeks postpartum. This relationship held true after we controlled for a number of factors that we know are associated with postnatal depression or perinatal depression and that includes factors like risk of - or existing depression or anxiety, tissue trauma during childbirth, lacerations, etc, and obesity.

We've also recognized that there is probably population heterogeneity in this relationship. We looked at groups of racial and ethnic populations, white; African-American; and non-Hispanics, whites, Latinos and others and found that there is variability in pain relief under epidural

analgesia between these two groups that points to heterogeneity at the population level and most likely highlights also intraindividual variability and pain expression and pain relief. What we still don't know are a couple of other things. So we know that certain polymorphisms or genetic polymorphisms and the expression of COMT, ADRB2 and oxytocin are influential in the progress of labor but what we don't really know are how these things when coupled with social and behavioral factors like a pain sensitivity profile, a person's personality, their social support network, how any of that is influential in labor pain or in the expression of depression in the postnatal period.

So in order to address that we are currently recruiting for a prospective observational study and we are looking at women who are choosing to use epidural analgesia in women who are not in order to try to tease out some of these factors and hopefully sometime in the future we will be able to report back to you with results.

Finally, perinatal pain can be very traumatic. Up to - there is evidence that up to 33% of women view this childbirth experience to have been traumatic in some way. And by 4 to 8 weeks these women are exhibiting at least 3 trauma symptoms. And when you really drill down into what is it that can predict these perceptions of birth trauma there are a number of thematic components that arise. One is a history of trauma and lack of social support, but importantly pain seems to be a factor here too. Not only pain during the first stage of labor but also a woman's pain expectation so that whatever she expected - if whatever she expected is met in reality by something out of proportion to that expectation this may be a nidus for birth trauma.

So in summary, for a subset of women labor pain and pain in the perinatal period may contribute to long term negative health consequences for both the mother and their children. There is tremendous interindividual variability in the predisposition toward and the expression of labor pain as well as depression, and we have a lot of work that needs to be done in order to identify specific interventions that will work best for specific women in whom more aggressive pain management strategies may be beneficial.