The Impact of Genetics and Other Factors on Intra- and Post-partum Pain

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Published online: 10 August 2013
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Abstract In an attempt to provide some explanation for the observed differences in pain perception and analgesic requirements during labor and delivery between women, the idea that genetic variability is an important factor has emerged over the past decade. Bearing in mind the challenges posed when evaluating pain during childbirth as a phenotype, recent findings in the field of genetics and obstetric anesthesia are presented in this review; in particular those related to differences in labor analgesia requirements between women, the response to opioids after cesarean delivery, as well as theories on why post-cesarean pain may be different from other types of post-surgical pain.

Keywords Labor pain · Cesarean delivery · Genetics · Polymorphism · Opioid · OPRM1

Introduction

Recent developments in genetic research have opened vast opportunities to expand and improve our understanding of how genetic variability impacts disease severity, and how pharmacogenomics has the potential to transform the way medicine is provided to offer individualized personalized care. Successful implementation of pharmacogenomics discoveries has already occurred in various medical disciplines, resulting in reduced side effects and improved drug

efficacy with cancer therapies, psychotropic agents and management of cardiovascular diseases.

Can these successes also be introduced in the field of obstetric anesthesia in order to improve our daily care of laboring women and provide tailored labor analgesia? In an attempt to provide some explanation for the observed differences in pain perception and analgesic requirements during labor and delivery between women, the idea that genetic variability may be an important factor has emerged in the past decade. If certain women are able to tolerate labor pain and ‘resist’ the temptation of a labor epidural, it may well be that they have a different genetic make-up that helps them endure childbirth pain or that certain genes improve the efficacy and analgesic response to pharmacological interventions.

Childbirth is one of the most desired event in many couple’s life and over 4 million deliveries are celebrated every year in the United States [1]. Therefore, the expectation that studying intra- and post-partum pain will be easy, feasible and straightforward is realistic. However, it is not uncommon nowadays for women to prepare a ‘birth plan’ with specific requests based on beliefs and expectations that often include a ‘natural childbirth’. ‘Natural childbirth’ probably means different things to different women. Often considered to represent a vaginal as opposed to a cesarean delivery, for some women “natural childbirth” implies a ‘non-medicated childbirth’ or simply ‘having a baby without an epidural’. This remains a perplexing observation for the well intended obstetric anesthesiologist that so many women prefer to suffer the ‘worst pain they will endure in their lifetime’ without enjoying the benefits of what we can so easily provide and consider to be safe: effective, low dose neuraxial analgesia [2]. It is even more surprising to find out that women who end up with a cesarean delivery, whether having first been in labor

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or not, report high pain scores and take non-trivial amounts of opioids for pain relief [3]. It is almost as if pain during the numerous and unpredictable (long) hours of labor followed by that during vaginal delivery was a desirable and tolerable type of pain that required no analgesics whatsoever, whereas that occurring after a relatively simple surgical procedure was unbearable and resulted in severe pain for most women despite multimodal analgesia.

Obviously, labor pain and post-cesarean pain represent two very distinct pain entities: labor representing the ultimate visceral and mechanical model of acute pain, while the somatic pain, pulling, tugging and stretching that typically occurs during cesarean delivery represents a surgical model of acute pain with potential chronic neuropathic features. Perhaps one should reconsider the entire question. Perhaps post-cesarean pain is very different from any other post-surgical pain, because women have different expectations, because their hormonal status is unique, and because analgesia until recently has been quite minimal due to concerns surrounding analgesia in breastfeeding mothers. Interestingly, very few studies have evaluated whether labor pain followed by a cesarean delivery actually increased post-cesarean pain and analgesic requirements, due to the combination of an incision superimposed on a ‘struggling’ laboring uterus, to the fatigue that often results from undergoing labor followed by a cesarean delivery and to the disappointment of not being able to deliver ‘naturally’ as planned.

One can only agree that the subjective ‘phenomenological’ context of childbirth, along with psychosocial, demographic and obstetrical factors result in labor pain being one of the most challenging phenotype to evaluate, quantify, compare and interpret. In most pain studies evaluating clinical pain, a numerical pain scale is used to score the intensity of pain, and the amount of pain medication required to manage pain is another crucial outcome. How can we measure pain when most women believe that labor pain should be untreated, and why have we believed for so long that we could capture the essence of labor pain and quantify its severity by asking women to rate their pain during contractions over hours on a scale from ‘no pain’ to the ‘worst imaginable’ when labor pain is so experiential?

Bearing in mind the challenges posed when evaluating pain during childbirth as a phenotype, recent findings in the field of genetics and obstetric anesthesia such as differences in labor analgesia requirements between women, the response to opioids after cesarean delivery and theories on why post-cesarean pain may be different from other types of post-surgical pain will be presented in this review. We will explore the exciting hypothesis that has recently emerged regarding the protective effect that central oxytocin may have on post-cesarean pain, resulting in a long-term protection from chronic pain after cesarean delivery.

Impact of Genetics on Labor Pain

Less than a handful of genes have so far been evaluated in the context of labor pain and analgesic response to systemic or neuraxial opioids; the two most well studied genes are the μ -opioid receptor gene (*OPRM1*) and the catechol-O-methyltransferase gene (*COMT*) gene (Tables 1 and 2).

The μ -Opioid Receptor Gene (*OPRM1*)

Despite numerous studies in the last two decades, the exact mechanism by which the most common and well studied polymorphism of *OPRM1* (A118G, p.40Asn/Asp) influences opioid analgesia remains unresolved and the relevance of this genetic variant for the clinician is somewhat unclear [4–6]. Nonetheless, recent findings suggest that the altered μ -opioid receptor may be associated with an enhanced effect in response to endogenous opioids, but a decreased response to exogenous opioids. In other words, individuals, carrying the G118 allele, should have a higher threshold to pain (due to increased sensitivity to endogenous opioids), but may require higher doses of μ -opioid agonists to achieve analgesia, and be at higher risk for opioid-induced side effects.

Factors that have made various studies difficult to interpret and findings difficult to generalize include sex-genotype interactions [7] and a large inter-ethnic variability in genotype distribution [8] with an ethnicity-dependent association of *OPRM1* genotype with pain sensitivity [9].

OPRM1 and Labor Pain

In a large retrospective observational study in a cohort of Swedish women ($n = 814$), enrolled over a period of three months, there was no association between A118G genotype and labor pain related behaviors [10]. The phenotype that was evaluated was composed of the following factors: (1) the cervical exam upon arrival in the labor room, and (2) the use of any type of analgesia (acupuncture, nitrous oxide, systemic opioids, epidural). In other terms, women did not seem to have different thresholds for labor pain or epidural request based on A118G genotype. Unfortunately, the response to labor analgesia in the form of systemic or epidural opioids was not evaluated, epidurals were placed at a relatively advanced stage in labor (6 cm of cervical dilatation), and the epidural rate was remarkably low (30 %), likely reflecting the institutional practice and overall national trends in obstetric anesthesia use. Therefore, the resulting lack of difference in epidural use between genetic groups is most likely the consequence of an overall low epidural rate and does not provide truly meaningful information with regards to genetic influences. Of note, the same investigators were also unable able to

Table 1 Genotype frequency of SNPs of interest for labor analgesia and post-cesarean pain

Gene	Nucleotide	Polymorphism	Genotype frequency by ethnicity		
			Caucasian	African-American	Asian
<i>OPRM1</i>	c.118A/G	rs1799971—p.40Asn/Asp	AA 65–70 % [8]	AA = 100 % [22]	AA = 35 % [24]
			AG 25–30 %	AG = 0	AG = 45 %
			GG 0–5 %	GG = 0	GG = 20 %
<i>COMT</i>	c.472G/A	rs4680—p.158Val/Met	GG = 22 % [19]	GG = 52 % [87]	GG = 62 % [88]
			GA = 47 %	GA = 44 %	GA = 32 %
			AA = 31 %	AA = 4 %	AA = 5 %
<i>CYP2D6</i>		80 SNPs affecting enzymatic activity	UM = 5–10 % [54]	UM = 40 % [54]	UM = 2–5 % [54]
		CYP2D6*1—normal	EM = 65–80 %	EM = 50 %	EM = 90 %
		CYP2D6*2—increased	IM = 10–15 %	IM = 9 %	IM = 5 %
		CYP2D6*3, *4, *5—none	PM = 5–10 %	PM = 1 %	PM = 2–5 %
		CYP2D6 *9, *10, *17—decreased			
<i>ABCB1</i>	c.3435C/T	rs1046542—synonymous p.1145Ile	CC = 24 % [89]	CC = 68 % [89]	CC = 31 % [52]
			CT = 48 %	CT = 31 %	CT = 51 %
			TT = 28 %	TT = 1 %	TT = 18 %

UM Ultra-rapid metabolizer

EM Extensive metabolizer

IM Intermediate metabolizer

PM Poor metabolizer

SNP Single nucleotide polymorphism

rs RefSNP

OPRM1 μ -opioid receptor gene

COMT Catechol-O-methyltransferase gene

CYP2D6 Cytochrome P450 2D6

ABCB1 ATP binding cassette sub-family B member 1 gene

find an association with a pain-protective haplotype of the guanosine triphosphate cyclohydrolase gene (*GCHI*) evaluating the same phenotype and labor pain related behaviors in their cohort of laboring women [11].

OPRM1 and Intravenous Fentanyl for Labor Analgesia

While the influence of A118G genotype on intravenous (IV) fentanyl has been evaluated in several studies mostly in Asian patients in the context of post-operative analgesia [12–18], only one study examined its effect for early labor analgesia [19]. However, fentanyl is often offered in North America to women in early labor in an effort to delay or avoid receiving neuraxial analgesia. Studying the influence of A118G genotype in this clinical context offers the potential to explore and compare the analgesic response to both IV and spinal fentanyl in the same woman under the same clinical conditions (i.e., labor pain).

In this North-American cohort ($n = 98$), most of whom were Caucasian, IV analgesic success was found to be relatively low; only 20 % of women reported a pain score of less than 10/100 at 15 min after dosing [19]. A118G genotype in combination with p.158Val/Met (c.472G/A) of

COMT seemed to have an impact on the analgesic outcome. Specifically, IV fentanyl was least effective in women with the A/A-Met/Met combination of *OPRM1* and *COMT*, which was carried by 18 % of women in this cohort. The study was not sufficiently powered to explore the hypothesis that spinal and systemic opioid dynamics are different and to determine whether enhanced analgesia in response to spinal fentanyl in the presence of the variant G118 allele might exist when an enhanced response to IV fentanyl did not.

OPRM1 and Spinal Fentanyl for Labor Analgesia

Three studies have evaluated the influence of A118G genotype on the response to spinal fentanyl given as part of a CSE analgesic for labor analgesia [20•, 21, 22].

The first was conducted in a Swiss cohort of nulliparous women ($n = 224$) requesting neuraxial analgesia early in labor [20•]. Using the up-down sequential allocation method, women carrying the G118 allele were shown to require substantially lower doses of spinal fentanyl than women without this allele. This finding was replicated with a different pharmacological study design using

Table 2 Clinical effects of genetic variants in the context of labor pain, labor analgesia response and post-cesarean pain

Genetic variant	Clinical context	Intervention	Outcome	
<i>OPRM1</i> A118G	Labor analgesia (CSE) (<i>N</i> = 224, Swiss)	Spinal fentanyl (2.5–30 mcg)	Analgesia requested at greater cervical dilatation Lower ED50 (1.5- to 2-fold) in women with G118 allele	[20•]
<i>OPRM1</i> A118G	Labor analgesia (CSE) (<i>N</i> = 190, North American)	Spinal fentanyl (25 mcg)	No effect of G118 on duration of spinal analgesia	[21]
<i>OPRM1</i> A118G	Labor analgesia (IV) (<i>N</i> = 98, North American)	IV fentanyl (1.5 mg/kg)	Study underpowered	[19]
<i>COMT</i> Val158Met	Labor analgesia (IV) (<i>N</i> = 98, North American)	IV fentanyl (1.5 mg/kg)	Joined allelic effect (least effective in A118-Met158 homozygotes)	[19]
<i>OPRM1</i> A118G	Labor analgesia (Epidural) (<i>N</i> = 57, Italian)	Epidural sufentanil (16–27 mcg)	Lower ED50 in women with G118 allele	[23]
<i>OPRM1</i> A118G	Labor pain and progress (<i>N</i> = 65, North American)	NONMEM analysis	Underpowered (also for experimental pain)	[49]
<i>OPRM1</i> A118G	Labor pain (<i>N</i> = 814, Swedish)	Analgesia (all types)	No difference in ‘labor pain behaviors’: Similar cervical dilatation upon arrival in labor room Similar epidural rate (in the order of 30 %)	[10]
<i>OPRM1</i> A118G	Cesarean pain (<i>N</i> = 103, North American)	Spinal morphine (150 mcg)	No effect of G118 on breakthrough pain and additional analgesics	[21]
<i>OPRM1</i> A118G	Cesarean pain (<i>N</i> = 588, Chinese)	Spinal/IV morphine (100 mcg)	Higher pain scores with G118 allele Higher morphine dose (IV PCA) with G118 allele in the 1st 24 h (after spinal morphine)	[24]
<i>OPRM1</i> A118G	Cesarean pain (<i>N</i> = 617 Chinese; <i>N</i> = 241 Malay; <i>N</i> = 136 Indian)	Spinal/IV morphine (100 mcg)	G118 homozygosity more frequent among Malay and Indian Multiple regression analysis showed pain scores predicted morphine dose, followed by ethnicity and A118G genotype Higher pain scores and morphine dose (IV PCA) among Indians in the 1st 24 h (after spinal morphine)	[25]
<i>OPRM1</i> A118G	Cesarean pain (<i>N</i> = 158, North American)	Hydrocodone	No effect on pain, side effects or hydrocodone dose	[50]
<i>CYP2D6</i>	Cesarean pain (<i>N</i> = 45, North American)	Codeine	Regression analysis showed that serum hydromorphone levels were correlated with enhanced analgesia, but only with A118 homozygosity	[51]
<i>ABCB1</i> C3435T	Cesarean pain (<i>N</i> = 620, Chinese)	Spinal/IV morphine (100 mcg)	Study underpowered PM (<i>N</i> = 2) no analgesia UM (<i>N</i> = 3) severe side effects No difference in morphine dose (IV PCA) in the 1st 24 h (after spinal morphine) Trend for higher incidence of persistent pain in TT women and significantly longer duration of pain	[52]

CSE combined spinal-epidural

IV intravenous

ED50 median effective dose (dose effective in 50 % of women)

NONMEM nonlinear mixed effects modeling

PM Poor metabolizer

UM Ultra-rapid metabolizer

OPRM1 μ -opioid receptor gene*COMT* Catechol-*O*-methyltransferase gene*CYP2D6* Cytochrome P450 2D6*ABCB1* ATP binding cassette sub-family B member 1 gene

random-dose allocation, confirming a twofold difference in spinal fentanyl requirement between genetic groups. Of note, cervical dilatation at the time of analgesia request was significantly less in the 118 AA women than that in women carrying one or two variant alleles (118 AG or 118 GG). The finding of lower analgesic requirements at a more advanced stage in labor is consistent with the principle that women carrying the *G118* allele may have higher pain tolerance that allows them to wait longer before requesting neuraxial analgesia.

In a 2nd study performed in a North American cohort of laboring women ($n = 190$), time from a spinal dose of fentanyl (25 mcg) until women requested additional analgesia was not influenced by A118G genotype [21], suggesting that this SNP may well influence spinal fentanyl potency without affecting the duration of analgesic action.

In the 3rd and most recent study, combining two ethnically distinct hospital centers [one from Israel ($N = 45$; mixed Jew/Arab) and one from the United States ($N = 80$; mixed Hispanic/African-American)], time from a spinal dose of fentanyl (20 mcg) until request for additional analgesia was not influenced by A118G genotype, nor did the onset of analgesia or the occurrence of itching differ between genetic groups [22]. The major difference was the duration of analgesia and the percent of women itching that was found when comparing women from different recruitment centers, highlighting the importance of ethnicity and cultural differences in pain outcomes.

OPRM1 and Epidural Sufentanil for Labor Analgesia

In an observational study evaluating a cohort of Italian nulliparous women ($n = 57$) using the same up–down methodology, women carrying the G118 allele had a significantly lower dose requirement (ED50) for epidural sufentanil. These data demonstrated a similar pharmacogenetic association of A118G genotype with neuraxial opioid potency during labor analgesia, although with a more modest clinical effect [23].

Of importance, these findings of a pharmacogenetic effect of A118G on spinal fentanyl or epidural sufentanil, with lower dose requirements in laboring women with the G118 allele, are in disagreement with most if not all other studies examining the influence of A118G genotype and opioid analgesia [6], whether one evaluates post-operative IV fentanyl consumption [12–18], spinal morphine for post-cesarean pain [21, 24, 25], IV morphine for post-operative pain [26–31] or oral morphine for chronic cancer pain [5, 32, 33].

Potential explanations for such discrepant results are that the physiology of and pathways triggered by labor pain are remarkably different from pathways triggered during

experimental, post-operative or chronic pain. Indeed, similar disparate results in human genetic studies of pain sensitivity have been shown to occur with other polymorphisms commonly assessed in pain studies [34]. Another potential explanation is that each opioid is affected differently and/or that the response to systemic rather than spinal fentanyl is affected differently by *OPRM1* genotype. Lastly, a recent study evaluating the response to different experimental modalities in healthy individuals found no significant effect of *OPRM1* genotype on pain sensitivity in the overall sample, but when each ethnic group was examined separately (Caucasians, Hispanics and African-Americans), lower pain sensitivity was found among Caucasians carrying the G118 allele, with a trend in the opposite direction among Hispanics and no measurable effect among African-Americans (the G allele is under-represented in this ethnicity) [9]. As there were no Asians in that study and the G118 allele is extremely common among Asians, studies comparing pain sensitivity and opioid response between Caucasians and Asians will be of added value. Also, it remains to be determined whether haplotype structure, gene–gene interactions, or DNA methylation [35], rather than the A118G genotype itself, are key to explain these inter-ethnic differences. Nonetheless, this ethnicity-dependent genetic association may contribute to some of the discrepancies reported in clinical studies as discussed above.

The Catechol-*O*-methyltransferase Gene (*COMT*)

The most well studied genetic variant of *COMT* is the p.158Val/Met (c.472G/A), which has been associated with pain sensitivity and various pain phenotypes. *COMT* regulates the metabolism of dopamine and noradrenaline, and high *COMT* activity as is the case with the Val158 allele, is associated with improved dopaminergic transmission and confers an advantage in the processing of aversive stimuli or stressful conditions (warrior strategy). The Met158 allele is associated with an advantage in memory and attention tasks (worrier strategy) [36]. Individuals homozygous for the Met158 allele display increased pain sensitivity but lower μ -opioid system activation during sustained pain [34, 37, 38] and the Met158 allele has been associated with chronic pain disorders [39, 40], acute post-operative pain [29, 41], chronic post-surgical pain [42], and opioid-induced hyperalgesia (OIH) [43]. The effect of *COMT* genotype on pain processing seems to become apparent only when pain modulation is challenged, such as occurs after repeated pain stimulation [44], or after remifentanyl exposure in healthy volunteers Met158 homozygous [43]. In a cohort of women with fibromyalgia, Met158 homozygotes displayed lower pressure pain thresholds and higher cold pain sensitivity [45].

COMT and Intravenous Fentanyl for Labor Analgesia

As previously mentioned in the study described above [19], A118G genotype of *OPRM1* appeared to influence the analgesic outcome only in combination with the Val158-Met genotype of *COMT*. Nonetheless, *COMT* genotype alone influenced the response to IV fentanyl; the average decrease in pain scores 15 min after a unique dose of IV fentanyl was lowest among women 158Met/Met (31 % of women) compared with that in women 158Val/Met or 158Val/Val. While there is no doubt that IV fentanyl is not a common practice for labor analgesia, such findings may have useful clinical implications, such as not offering IV fentanyl in labor to women who will most likely not benefit from it.

These findings highlight the challenges in interpreting genetic association studies, in general, and in particular, when several SNPs are examined jointly [46, 47]. The major challenge remains to design studies with a crisp phenotype in the context of labor pain. [48]. Most existing studies seem to have been underpowered [19, 49], or to not have taken into account ethnic and cultural differences [22] or the impact of hospital and local practice [10].

Impact of Genetics on Post-cesarean Pain and Analgesia

Only a handful of clinical studies have examined the influence of pain genes on acute post-operative pain, opioid consumption and chronic pain and these have focused on the A118G genotype of *OPRM1* [21, 24, 25, 50] (Table 2). Other candidate genes that have been examined in the context of cesarean deliveries include the response to codeine according to *CYP2D6* genotype [51] and to acute and chronic pain after cesarean delivery according to ATP-binding cassette, sub-family B member 1 (*ABCB1*) genotype [52] (Table 2).

OPRM1 and Post-cesarean Analgesia

In Chinese women ($n = 588$) undergoing elective cesarean deliveries under spinal anesthesia (with morphine 100 mcg, no fentanyl), pain scores and IV PCA morphine use 24 h post-operatively were significantly lower in women A118 homozygous [24]. Distribution of IV morphine use over time (doses were recorded in 4 h time intervals) demonstrated that most of morphine use occurred during the first 4 h after spinal anesthesia. It is possible that this early IV morphine use reflects lack of analgesia upon arrival in the post-anesthesia care unit; indeed onset of analgesia procured by spinal morphine is known to be slow and can occur up to 45 min after its administration [53].

Consequently, initial differences in IV morphine use may be due to differences in pain perception rather than impaired spinal morphine analgesia in women carrying the G118 allele.

In a second report from the same institution, three different ethnic groups were evaluated ($n = 617$ Chinese, $n = 241$ Malays and $n = 136$ Indians) [25]. There were significant differences in genotype distribution between ethnic groups (G118 homozygosity was more frequent among Malays and Indians than among Chinese women). The authors reported a large inter-individual range as 65 women did not take any IV morphine and the highest dose was 62 mg. Nonetheless, the average dose of self-administered morphine over 24 h was low (<10 mg). In a multiple regression analysis, the most important factor contributing to morphine dose was maximum pain score, followed by ethnicity and A118G genotype. After correction for genotype, ethnicity was still a significant contributing factor, with Indian women reporting higher pain scores and using higher IV morphine doses.

A third study evaluated post-cesarean analgesia according to A118G genotype after a spinal dose of morphine 150 mcg and fentanyl 15 mcg, in a cohort of North American women ($N = 103$) [21]. The study design was substantially different from the two previous studies conducted on Asian women, and, therefore, the findings are not comparable. Women were not given an IV PCA for morphine use, and there was no difference in the duration of spinal morphine analgesia (on average 22 h) or need for analgesic supplementation over 72 h between genotypic groups. The incidence of nausea was similar between groups, however pruritus was less frequent in carriers of the G118 allele during the first 24 h.

In a recent study, post-cesarean analgesia with oral hydrocodone was evaluated according to A118G genotype in a North American cohort ($n = 158$) [50]. This study was designed to compare analgesic and side effect profiles, according to A118G genotype, with quantitative serum opioid concentrations, as well as total opioid consumption. The potential role that hydromorphone, an opioid metabolite of hydrocodone, may play in the analgesic response to hydrocodone was also evaluated. The study has several limitations, including the fact that the clinical protocol was changed after the first 40 cases were enrolled (spinal morphine was added thereafter and post-operative pain regimen changed) and that 43 women had opioid not derived from hydrocodone that was detected in the serum samples (suggesting these patients violated the study protocol). There was no difference in pain scores or hydrocodone doses between genotypic groups, although regression analysis revealed that in women A118 homozygous but not those carrying the G118 allele, analgesia correlated with hydrocodone dose and serum hydromorphone

but not hydrocodone levels. These results suggest that enhanced hydrocodone analgesia with A118 homozygosity is due to an enhanced response to its active metabolite, hydromorphone, rather than to a direct effect of A118G genotype on the response to hydrocodone. Since *CYP2D6* genotype was not specifically examined, one cannot evaluate the combined effect of A118G and *CYP2D6* genotypes, or of a gene–gene interaction, nor can one extrapolate this finding to non-obstetric cohorts.

CYP2D6 Genotype

Cytochrome P450 enzymes (CYPs) play a major role, as these are responsible for about 80 % of phase I metabolism, and *CYP2D6* metabolizes approximately 25 % of frequently used drugs. Individuals are classified as ultra-rapid (UM), extensive (EM), intermediate (IM) and poor (PM) metabolizers according to *CYP2D6* activity, and there is a large variability in the frequency of UM and PM based on ethnicity [54]. Codeine was formerly commonly given for pain management after cesarean deliveries, as it is classified as a weak opioid by the World Health Organization (WHO), and as such was considered safe in the context of breastfeeding mothers. However, the death of a breastfed 13-day-old neonate following a morphine overdose because his mother, an UM, was taking codeine after childbirth [55] resulted in a recent FDA warning on codeine use in nursing mothers [56]. Indeed, toxic blood levels of morphine or its active metabolite morphine-6-glucuronide (M6G) may arise in mothers and neonates that are *CYP2D6* UM or EM, because codeine is a pro-drug transformed by *CYP2D6* into its active substance, morphine.

In addition, *CYP2D6* induction, during pregnancy and the postpartum period, may impact the generation of active opioid metabolites such as morphine after the administration of codeine, or that of oxycodone, tramadol, and hydrocodone, respectively [57].

Overall, the level of evidence linking gene variation (*CYP2D6*) to phenotype (increased biotransformation of codeine into morphine) is significant; however, there is no randomized clinical trial assessing the benefits of genetic testing prior to codeine therapy at large [58]. While failure of analgesia with codeine can be well predicted by genotyping alone in individuals that are PM, predicting extremely high morphine formation still requires the effort of combining genotyping with phenotyping [59]. Recently formed, the clinical pharmacogenetics implementation consortium (CPIC) [60•] has established clinical recommendations for drug dosing based on genetic testing for only eight different drugs to date. The prescription of codeine according to *CYP2D6* genotype is one that may be relevant to the practice of obstetric anesthesia [61•].

CYP2D6 and Codeine for Post-cesarean Analgesia

In a recent pilot study in North American women ($n = 45$) receiving codeine for post-cesarean pain, analgesia according to *CYP2D6* genotype was evaluated [51]. Only five patients carried extreme genotypes (two PMs and three UMs) and the study was overall underpowered. Nonetheless, as expected, codeine was ineffective in the two PMs and codeine related side-effects were noted in two out of three UMs.

Prediction of codeine toxicity in neonates and their mothers using maternal genetic markers is complex, and a recent study in a predominantly Caucasian cohort ($n = 111$) showed that *CYP2D6* and *ABCB1* genotypes, but not that of *OPRM1* and *COMT*, were associated with codeine-induced CNS depression in neonates and their mothers [62]. However, because safer and more effective analgesic alternatives do exist, avoiding codeine in breastfeeding mothers is the current clinical recommendation [55, 63].

ATP-binding Cassette, Sub-family B Member 1 (*ABCB1*)

The ATP-binding cassette B1 (*ABCB1*) gene encodes the efflux transporter P-glycoprotein (P-gp) which is a key determinant of the bioavailability of many opioids (i.e., fentanyl, sufentanil, alfentanil, morphine-6-glucuronide and morphine-3-glucuronide). P-gp is a drug efflux transporter that functions at the blood–brain-barrier to limit the availability of morphine in the central nervous system, and could potentially affect pain perception and the response to opioids.

There are few clinical studies to date evaluating the influence of *ABCB1* genotype on pain and opioid analgesia [5, 16, 28, 30, 52, 64, 65]. Most studies have not found *ABCB1* genotype to be associated with major differences in pain outcomes, although P-gp activity is reduced in individuals TT homozygous for the C3435T polymorphism resulting in higher morphine CSF concentration [66] and potentially lower morphine consumption.

ABCB1 and Post-cesarean Analgesia and Chronic Pain

In a cohort of Chinese women ($n = 620$) undergoing an elective cesarean delivery with spinal anesthesia with morphine 100 mcg, pain scores and IV PCA morphine consumption was evaluated for 24 h, and chronic pain was assessed with phone questionnaires up to six months post-cesarean [52]. Three polymorphisms of *ABCB1* were evaluated: C1236T, G2677T/A and C3435T. Pain scores and morphine use for breakthrough pain were overall low. There was no difference in pain scores, IV PCA morphine dose, or incidence of side effects in the 1st 24 h post-cesarean between genotypic groups. Among the 503 women that

were followed up to six months post-cesarean, only 20 (4 %) had pain that lasted for longer than three months, and at six months, only 18 (3.6 %) reported still having pain at the site of the surgical incision. Women with the TT genotype of C3435T were more likely to report persistent pain after cesarean delivery (a nonsignificant trend) and duration of pain in these women was longest, of note, the C3435T genotype was carried by 18 % of women.

Chronic Pain After Cesarean Delivery

The incidence of chronic pain after surgery has been shown to depend on the surgical procedure and to range between 4 and 50 % [67]. The incidence of chronic pain after abdominal hysterectomy via Pfannenstiel is on the order of 10–15 % [68, 69], so one could anticipate that chronic pain after cesarean delivery would be in the same range, given the similarity of the procedure. However, recent prospective studies have identified that the incidence and severity of reported pain after cesarean delivery is remarkably low [70•, 71••], or quasi inexistent [72•, 73].

Based mostly on retrospective surveys and a few prospective studies, risk factors for chronic pain post-partum include personal characteristics (e.g., genetic susceptibility), pre-operative factors (e.g., menstrual pain, chronic pain), intra-operative factors (e.g., length of incision, uterine exteriorization, general anesthesia) and post-operative factors (acute pain, postpartum depression).

Studies attempting to characterize the type of pain persisting after cesarean delivery have identified that it is mostly neuropathic [74] as is largely described for persistent post-surgical pain in the general population [75, 76]. In addition, the presence of pre-operative scar hyperalgesia in women undergoing a repeat cesarean delivery predicts acute post-operative pain [77•] and may be associated with persistent pain.

Role of Oxytocin in Preventing Chronic Pain After Cesarean Delivery

One of the proposed mechanisms to explain the remarkably low incidence of chronic pain after cesarean delivery compared with that after other types of surgical procedures including hysterectomies, is that endogenous secretion of oxytocin during labor and delivery may confer protection.

Oxytocin is primarily synthesized in the paraventricular nucleus and the supraoptic nucleus of the hypothalamus. The paraventricular nucleus projects nerve fibers excreting oxytocin to various areas of the central nervous system including the spinal cord. In the spinal cord, nociceptive afferent messages originating from C and Aδ primary afferents are inhibited by a pathway that begins with

oxytocin being released from the paraventricular nucleus, and exciting a subpopulation of glutamatergic interneurons in the most superficial layer of the dorsal horn projecting in the lamina I–II, which subsequently distribute their excitation to all GABAergic neurons. In numerous animal models, oxytocin has long been shown to possess antinociceptive effects [78–83]; intrathecal administration of oxytocin prevents long-term potentiation in the dorsal horn, thought to be an important mechanism of enhanced central pain processing.

Recent experiments in rats to examine the potential protective effect of oxytocin during pregnancy suggest that spinal oxytocin release in the postpartum period has a key role in reversing hypersensitivity secondary to nerve injury [84•]. Protection seems to occur if and when surgery is performed around the time of delivery, and becomes apparent in the postpartum period, suggesting that the oxytocinergic pathway may not influence labor pain per se. In addition, examining bulbospinal descending pathways, spinal cord glial activation, and proteins that are upregulated in the spinal cord in females only, multiple sites of protection from chronic pain have been identified, with sex-specific responses in the spinal cord glia which may confer protection from injury induced chronic pain during childbirth [85].

More research is needed to understand and substantiate the antihyperalgesic effects of endogenous oxytocin at the time of delivery and to examine the potential use of intrathecal oxytocin to reduce chronic post-surgical pain. In addition, the oxytocin system represents an extremely promising target for novel central nervous system drug development, and considerable research is evaluating the role that central oxytocin may have with the potential to treat a large array of brain disorders [86].

Conclusions

Evaluating labor pain, the response to labor analgesia, acute post-cesarean pain and pain that persists beyond the expected time of recovery after childbirth has proven to be complex and challenging. Finding relevant genetic associations in this clinical context is particularly complicated, because genotyping without robust phenotyping is meaningless.

Lessons learned from genomic studies in the field of pain are numerous. Pain is not a unique single entity; therefore, the impact of genetic variants may be different according to the pain model (experimental, labor, incisional, inflammatory, neuropathic) and the individuals being tested (sex, ethnicity, age, co-morbidities). Sex-genotype and ethnicity-dependent genetic interactions have been shown to exist, indicating that one cannot generalize findings from different cohorts and extrapolate from one study population to another. Lastly, severe pain does not

necessarily predict higher analgesic requirements, because some genes increase pain sensitivity but at the same time enhance the response to opioids (e.g., *COMT*). There is currently no one single gene that can be associated with severe labor pain, or predict post-cesarean pain or chronic pain after childbirth. Pharmacogenetic studies have identified polymorphisms that influence the response to opioids and researchers are still in the process of evaluating the clinical relevance of such genetic associations. The only clinical recommendation that has been made based on pharmacogenetic testing is to avoid codeine in breastfeeding mothers unless it has been established that the mother is not an ultra-metabolizer for CYP2D6.

Finally, novel and exciting research is now focusing on the possible protective role of oxytocin in the development of chronic pain. Oxytocin, a hormone and neurotransmitter also known to influence social and emotional processing such as trust, bonding and empathy may not only reveal how psycho-social context might actually protect women from developing chronic pain after childbirth, but more importantly, provide one more clue in understanding the bio-psycho-social nature of pain.

In the meantime, standard tools and criteria to better define labor pain and persistent incapacitating pain need to be adapted to the obstetric population. Since cesarean deliveries constitute a unique surgical model and some women undergo multiple cesarean deliveries, over the course of several years, this offers the opportunity to perform longitudinal pain testing with robust pain phenotyping.

Compliance with Ethics Guidelines

Conflict of Interest Ruth Landau has received funding for research projects not related with the topic of this review from the Millennium Research Institute (Millennium Laboratories), and is the recipient of a Swiss National Foundation Research Grant (SNF #3200B0-114129) that funded, in part, the *OPRM1* genetic research conducted in Switzerland. Clemens M. Ortner and Pascal H. Vuilleumier declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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