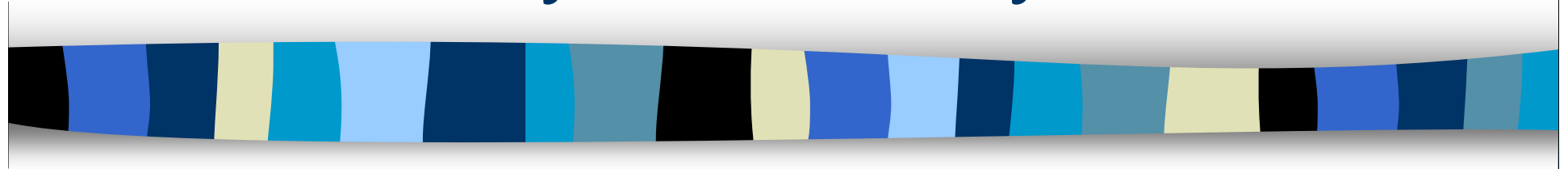


Neuropathic pain after cesarean section: myth or reality?



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IASP®

International Association for the Study of Pain®

Global Year Against Pain in Women

real women, real pain



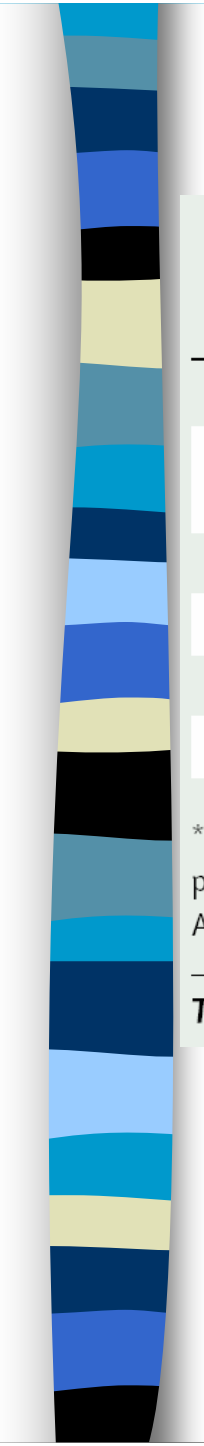
real women, real pain

Global Year Against Pain
2007-2008



Chronic pain

- Female (40%) > Male (31%)
 - IASP Clinical Update 2003
- 20% of patients implicated surgery
 - ↳ 50% sole cause
 - Macrae 2001
- Acute postoperative pain
 - 10-50% persistent pain



	Estimated incidence of chronic pain	Estimated chronic severe (disabling) pain (>5 out of score of 10)	US surgical volumes (1000s)†
Amputation ²	30–50%	5–10%	159 (lower limb only)
Breast surgery (lumpectomy and mastectomy) ³	20–30%	5–10%	479
Thoracotomy ⁴⁻⁷	30–40%	10%	Unknown
Inguinal hernia repair ⁸⁻¹⁰	10%	2–4%	609
Coronary artery bypass surgery ¹¹⁻¹³	30–50%	5–10%	598
Caesarean section ¹⁴	10%	4%	220

*Gall bladder surgery not included, since preoperative diagnosis of pain specifically from gall bladder is difficult and persistent postoperative pain could therefore be related to other intra-abdominal disorders. †National Center For Health Statistics, Ambulatory and Inpatients Procedures, USA, 1996.

Table 1: Estimated incidence of chronic postoperative pain and disability after selected surgical procedures*

Kehlet Lancet 2006;367:1618-25



Chronic pain: definition

Macrae 2001

- The pain developed after a surgical procedure
- The pain is of at least 2 months duration
- Other causes for the pain should have been excluded (e.g. continuing malignancy or chronic infection)
- The possibility that the pain is continuing from a preexisting problem must be explored and exclusion attempted
- CS: non-cyclic pain (not in relation with hormonal variations)



Chronic pelvic pain

- 15-25% females 30-50 years
 - Gynecological surgery (92%)
 - Hysterectomy (36%)
 - Weijenborg 2007
 - Cesarean section (67.2%)
 - Almeida 2002



Chronic pain following Caesarean section

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Departments of ¹Anesthesiology and ²Gynaecology and Obstetrics, Viborg Hospital, ³Danish Pain Research Center, University of Aarhus, and ⁴Department of Surgical Gastroenterology, Hvidovre Hospital, University of Copenhagen, Denmark

Acta Anaesthesiol Scand 2004; 48: 111-116

- 244 patients
- 18 % continued to have pain > 3 months after CS
- 12.3 % → still had pain 10 months after surgery
 - with almost 4% of them having constant pain

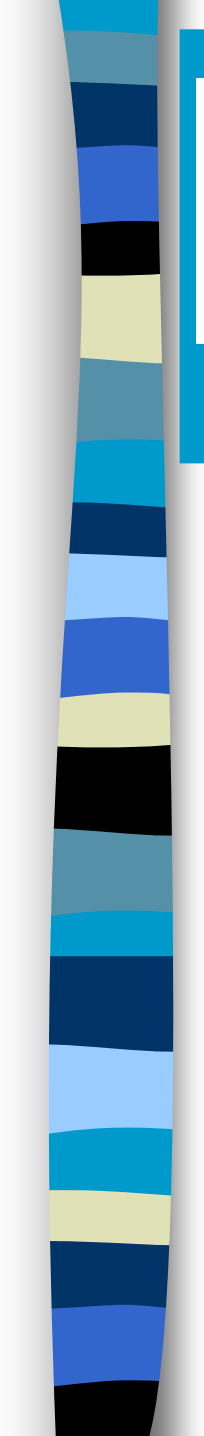


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American Journal of Obstetrics and Gynecology (2006) **194**, 1596–603

- 120 patients - spinal anesthesia
- Determine if Mg Sulfate decreases postoperative pain and analgesics consumption
- **16%** of patients → persisting wound or abdominal pain at 6 weeks



Postoperative Analgesic Effects of Continuous Wound Infiltration with Diclofenac after Elective Cesarean Delivery

Patricia M. Lavand'homme, M.D., Ph.D.,* Fabienne Roelants, M.D.,† Hilde Waterloos, R.N.,‡ Marc F. De Kock, M.D., Ph.D.§

Anesthesiology 2007; 106:1220-5

- 92 patients - spinal anesthesia
- 48h continuous intrawound infusion with diclofenac, ropivacaine or saline + PCA morphine
- Average incidence of **12 %** of residual pain at 6 months for the 3 groups



Postoperative Analgesic and Antihyperalgesic Effects of Spinal Clonidine administered during elective Cesarean section

P.M. Lavand'homme, F. Roelants, h. Waterloos, V. Collet, M. De Kock

Anesthesia Analgesia 2008 In Press

- 96 patients - spinal anesthesia
- Evaluated the postoperative antihyperalgesic effect of spinal clonidine
- Average incidence of residual pain:
 - 14% at 3 months
 - 7% at 6 months



Pain After Delivey (PAD) Study

Pan P ASA Meeting 2007 A 1203

- 4 medical institutions located in NC and NY, USA, Geneva and Brussels
- 2518 patients enrolled, 1861 evaluable
- **9.2 %** residual pain at 8 weeks after CS
 - Site of incision and back
 - 50%: pain affecting at least 1 or more daily activities (walking, mood, sleep, relations to others or ability to concentrate)



Real problem...

- CS = the most common major surgical procedure in the world
- Incidence ↑ in developed and developing world ≈ 20 -25 %
 - 1937 → 3%
 - 1990 → 12%
 - 2000 → 20-25% in US, UK
 - 2007 → 20% in France
 - 29.2% in Switzerland (2004)



Real problem...

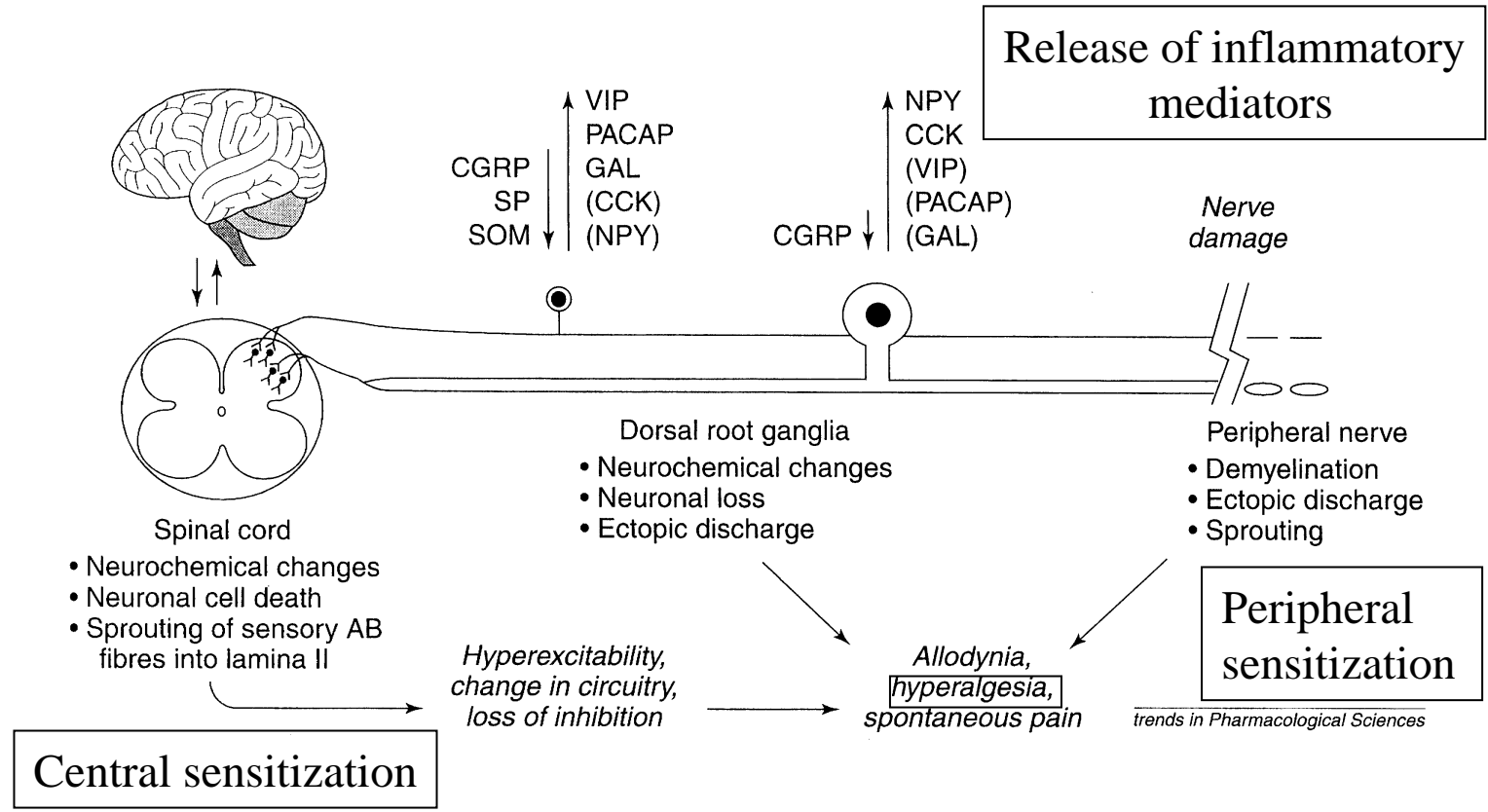
- To have an exact idea of the problem, we have to consider the number of procedure
- US → 1.1 million CS (2002)
 - 5 % chronic pain affecting at least 1 or more daily activities → 55 000 women
- Switzerland → 72 000 births (2003)
 - 20 000 Cesarean Section
 - 1000 women with chronic pain



Persistent postsurgical pain

Kehlet 2006

- Resembles to neuropathic pain
- Continuous inflammatory response can contribute to a maintained inflammatory pain



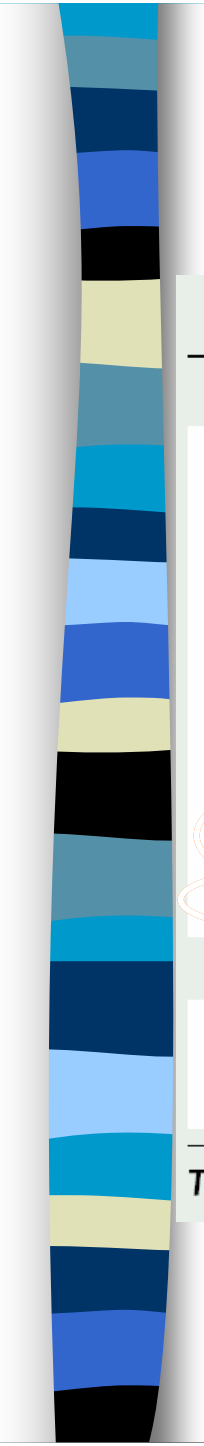


Differentiation of causes

- Neuropathic versus non-neuropathic



- Patient's description of the pain
To differentiate
neuropathic pain from inflammatory pain



	Neuropathic pain	Inflammatory pain
Positive symptoms and signs		
Spontaneous pain in damaged area	Yes	Yes
Heat hyperalgesia	Rarely	Often
Cold allodynia	Often	Rarely
Hyperpathia (increased threshold and explosive suprathreshold pains)	Often	Never
Aftersensations	Often	Rarely
Paroxysms	Often	Rarely
Burning pain	Often	Rarely
Throbbing pain	Rarely	Often
Negative symptoms and signs		
Sensory loss in damaged nerve territory	Yes	No
Motor deficit in damaged nerve territory	Often	No

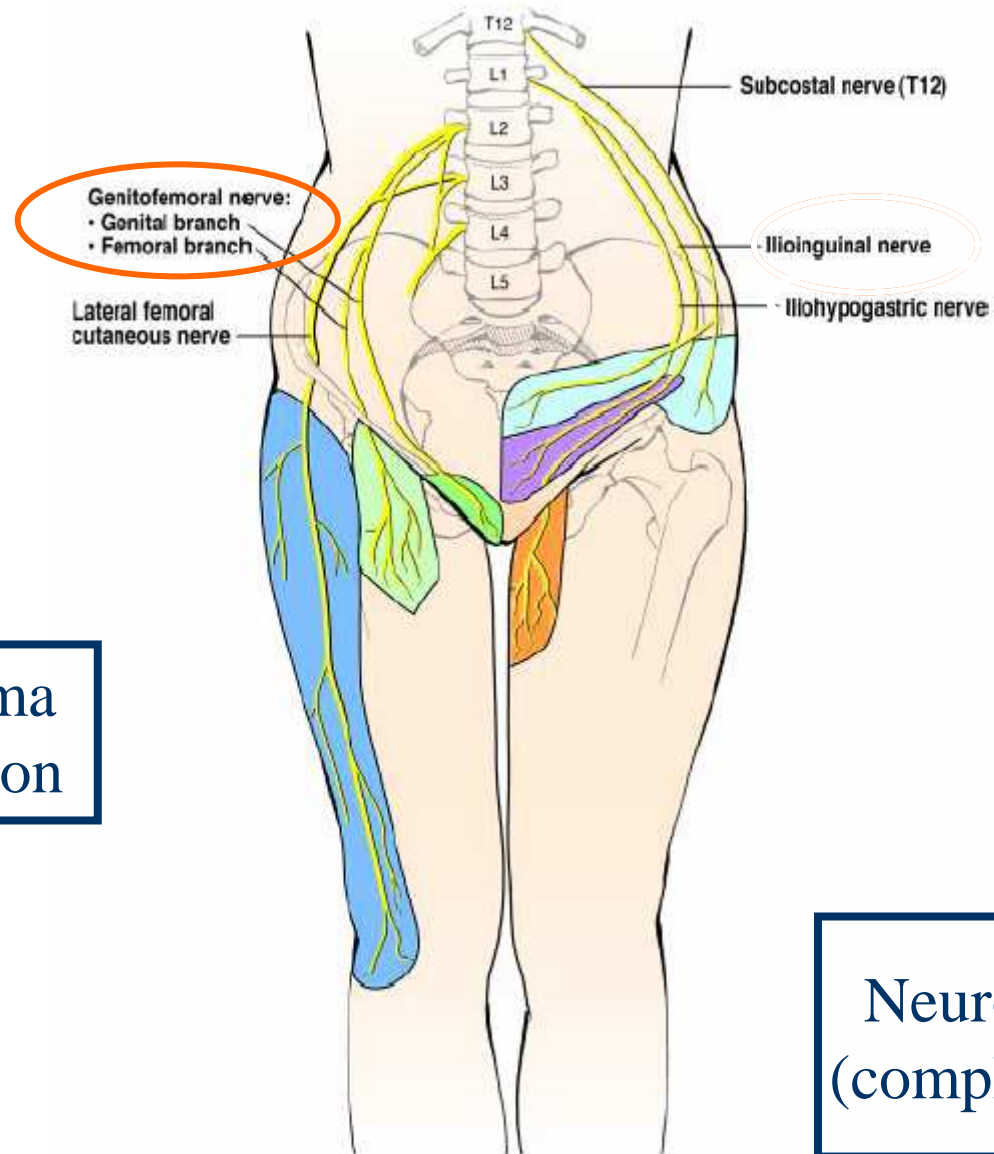
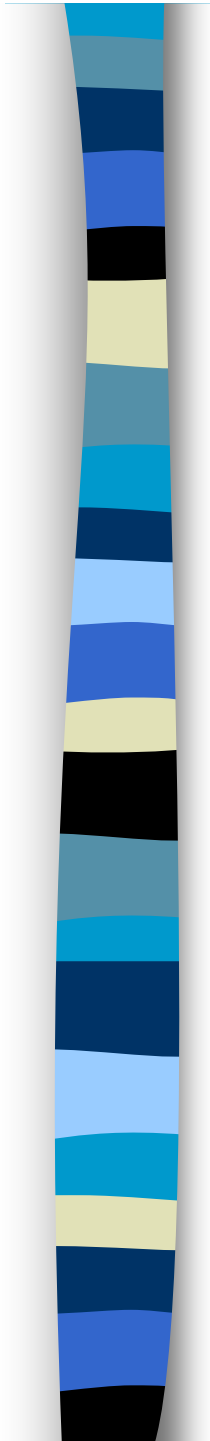
Table 2: Characteristic features of neuropathic and inflammatory pain



Other possible causes of postoperative chronic pain after CS

- Anatomic distorsion of pelvic structures
- Adhesions involving bladder, round ligaments and adjacent structures
- Myofascial pain due to nerve bundle injury and formation of neuromas (site incision)

Almeida 2002



Neuroma formation

Neuroma resection
(complete pain relief)

Fig. 1. Diagram of the major peripheral nerves that can be involved in chronic groin pain related to obstetric and gynecologic surgery.

Ducic. Algorithm for Intractable Postoperative Pain. Obstet Gynecol 2006.

Persistent pain : risk factors

- Severity of postoperative acute pain

Postoperative

- Type of anesthesia

- Surgical technique

Intraoperative

- Genetic susceptibility

- Preceding pain

- Psychosocial factors

- Others

Preoperative





Acute postoperative pain = The most prominent factor

- Association between the intensity of acute postoperative pain and subsequent development of chronic pain after surgery
- Nikolajsen: higher recall of severe postoperative pain when persistent pain
» *Acta Anaesthesiol Scand 2004*
- PAD study: 16.5% of operative-deliveries reported having severe postpartum pain ($\geq 7/10$) while in hospital
» *Landau R ASA Meeting 2007 A662*

PAD study

Pan P ASA Meeting 2007 A 1203

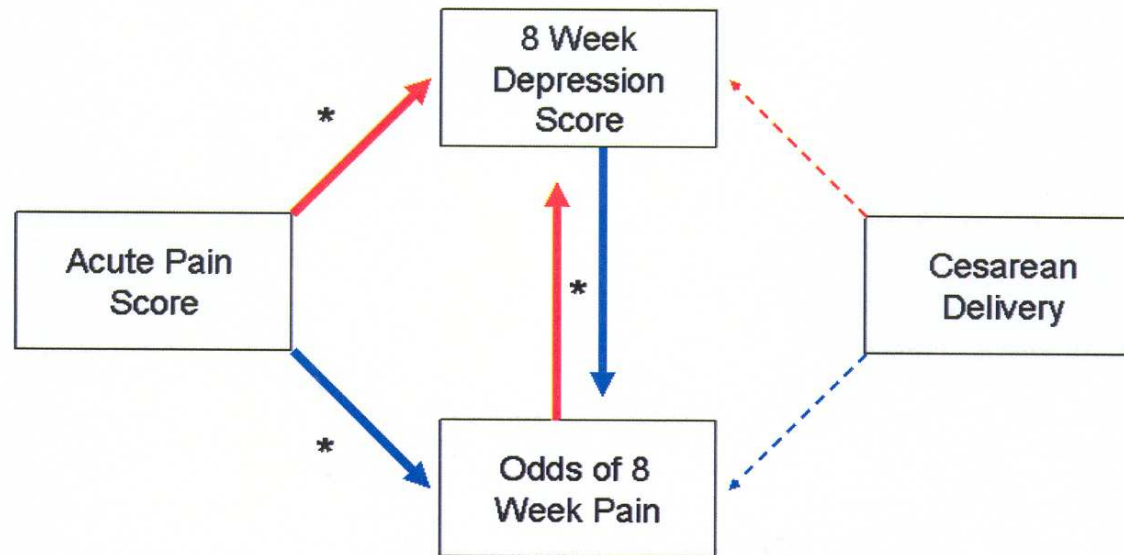


Figure 3. Interrelationships among delivery variables (mode of delivery and acute postpartum pain) and the 8 week outcomes (persistent pain and depression scores).

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Preoperative





Type of Anesthesia

■ General >< Spinal anesthesia

- Noxious inputs reaching the CNS are less during spinal anesthesia than during general anesthesia

» *Nikolajsen Acta Anaesthesiol Scand 2004*

■ Insufficient anesthesia and need of additional analgesia or GA

» *PAD study Landau R ASA Meeting 2007 A662*

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Preoperative





Surgical technique

- Frequency of chronic pain much higher after major operations (major nerve damage)
- Type of incision:
 - The length of Pfannenstiel incision (signs of nerve entrapment)
 - » *Luijendijk Ann Surg 1997*
 - Non-closure of both visceral and parietal peritoneum (↓ postoperative pain)
 - » *Rafique Br J Obstet Gynaecol 2002*
 - Midline incision vs Pfannenstiel: No!

Persistent pain : risk factors

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Genetic susceptibility

- Sensitivity to physiological nociceptive and clinical pain
- Differential heritable susceptibility
 - Generation and experience of pain
 - Response to analgesics

Persistent pain : risk factors

- Severity of postoperative acute pain

Postoperative

- Type of anesthesia

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Intraoperative

- Genetic susceptibility

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- Psychosocial factors

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Preoperative





Preceding Pain

- Previous pain correlates with the development of chronic neuropathic pain

Persistent pain : risk factors

- Severity of postoperative acute pain

Postoperative

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- Genetic susceptibility

- Preceding pain

- Psychosocial factors

- Others

Preoperative



Psychosocial factors

Expectation of pain

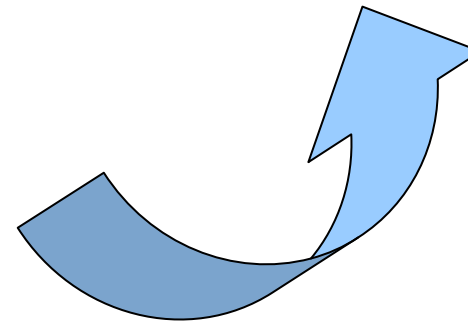
Fear, anxiety

Past memories

Social environment

Work and level of activities

response to noxious stimuli



Pain is the result of an interaction between biological and psychological variables

Persistent pain : risk factors

- Severity of postoperative acute pain

Postoperative

- Type of anesthesia

- Surgical technique

Intraoperative

- Genetic susceptibility

- Preceding pain

- Psychosocial factors

- Others

Preoperative





Other factors < PAD study

Pan P ASA Meeting 2007 A 1203

- Patients at risk of chronic postpartum pain
 - Pain with menstruation
 - Cesarean section for dystocia



Studies designed to try to prevent persistent pain

**Does magnesium sulfate reduce the short- and long-term requirements for pain relief after caesarean delivery?
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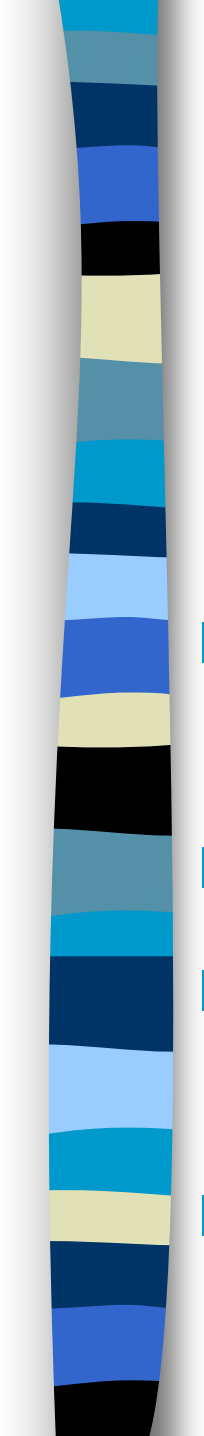
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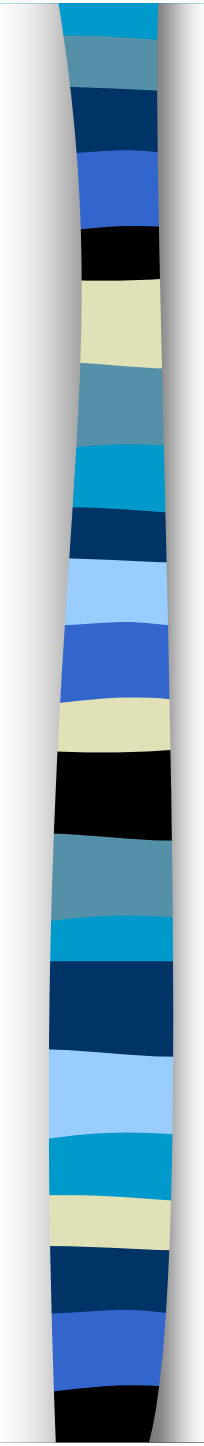


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- Mg Sulfate= antagonist of NMDA receptor in the spinal cord
- Alters pain processing
- ↓ induction and maintenance of central sensitization from nociceptive stimulation
- Implication:
 - prevention of persistent pain ?

- 
- Spinal injection: 0.5% hyperbaric bupivacaine + 15µg fentanyl
 - 120 patients - 3 groups - IV magnesium sulfate

Groups	Loading dose	after	n
High dose	50mg/kg	2g/h	42
Low dose	25 mg/kg	1g/h	38
Control	saline	saline	40

- All solutions commenced 1h before surgery and continued for 24h

No effects on early postoperative opioid requirement or pain after CS

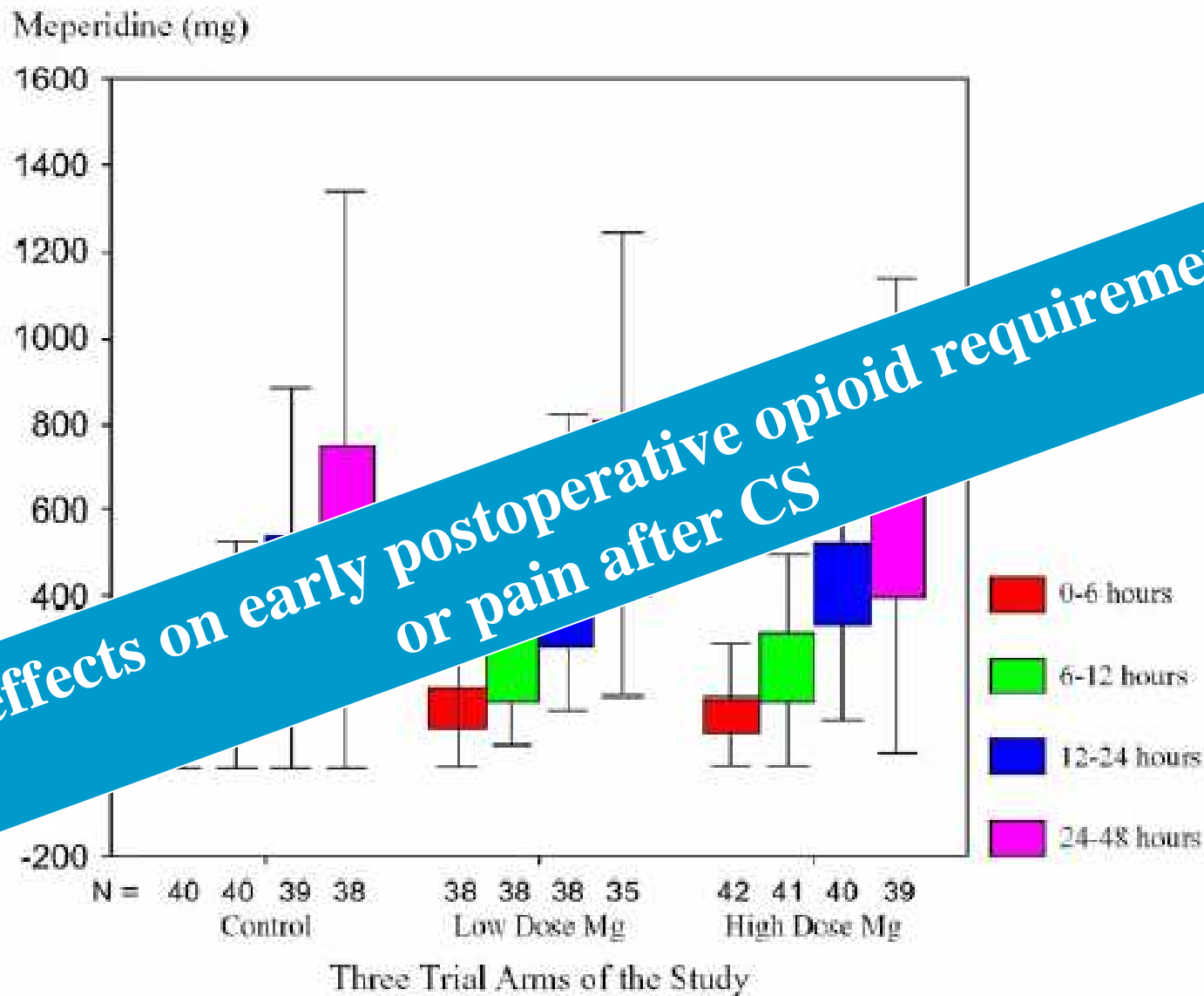


Figure Cumulative meperidine dose ≤ 48 hours postoperatively. *Mg*, Magnesium sulfate.



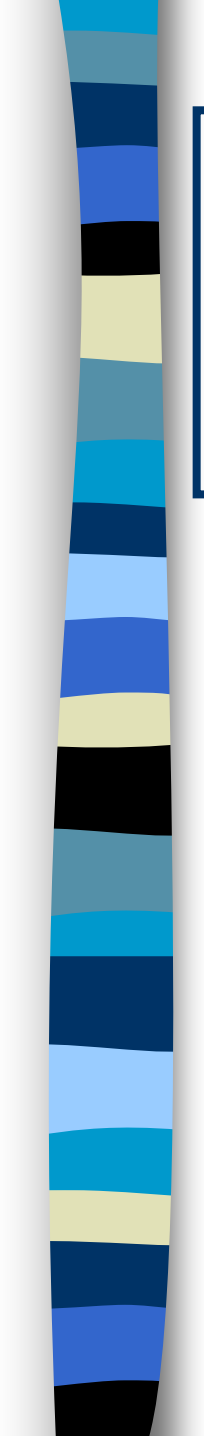
Results

- 8% → punctate mechanical hyperalgesia (von Frey filaments)
- 16% → persistent wound or abdominal pain at 6 weeks
 - low severity (no analgesics)
 - no difference between the groups



Conclusions

- Mg Sulfate does not reduce the severity of short- and long-term pain after cesarean delivery



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- Explore different analgesic regimens covering the entire perioperative period:
 - Systemic opioids - NSAID_s
 - Continuous wound irrigation with LA:
 - relieve pain by direct inhibition of noxious impulses from the site of injury
 - Continuous wound irrigation with NSAID_s:
 - ↓ local expression of mediators (PGs) that sensitize nociceptors on afferent fibers



Secondary goal

- Impact on:

- Prevention of central sensitization
- Persistent pain at 1-6 months after surgery

- 
- Spinal anesthesia – 0.5% hyperbaric bupivacaine + sufentanil

	Group Ropi	Group Diclo	Group Saline
n	30	30	30
intrawound	Ropi 0.2%	Diclofenac 300mg/48h	saline
IV	Diclofenac	saline	Diclofenac

- All patients received the same total dose of diclofenac

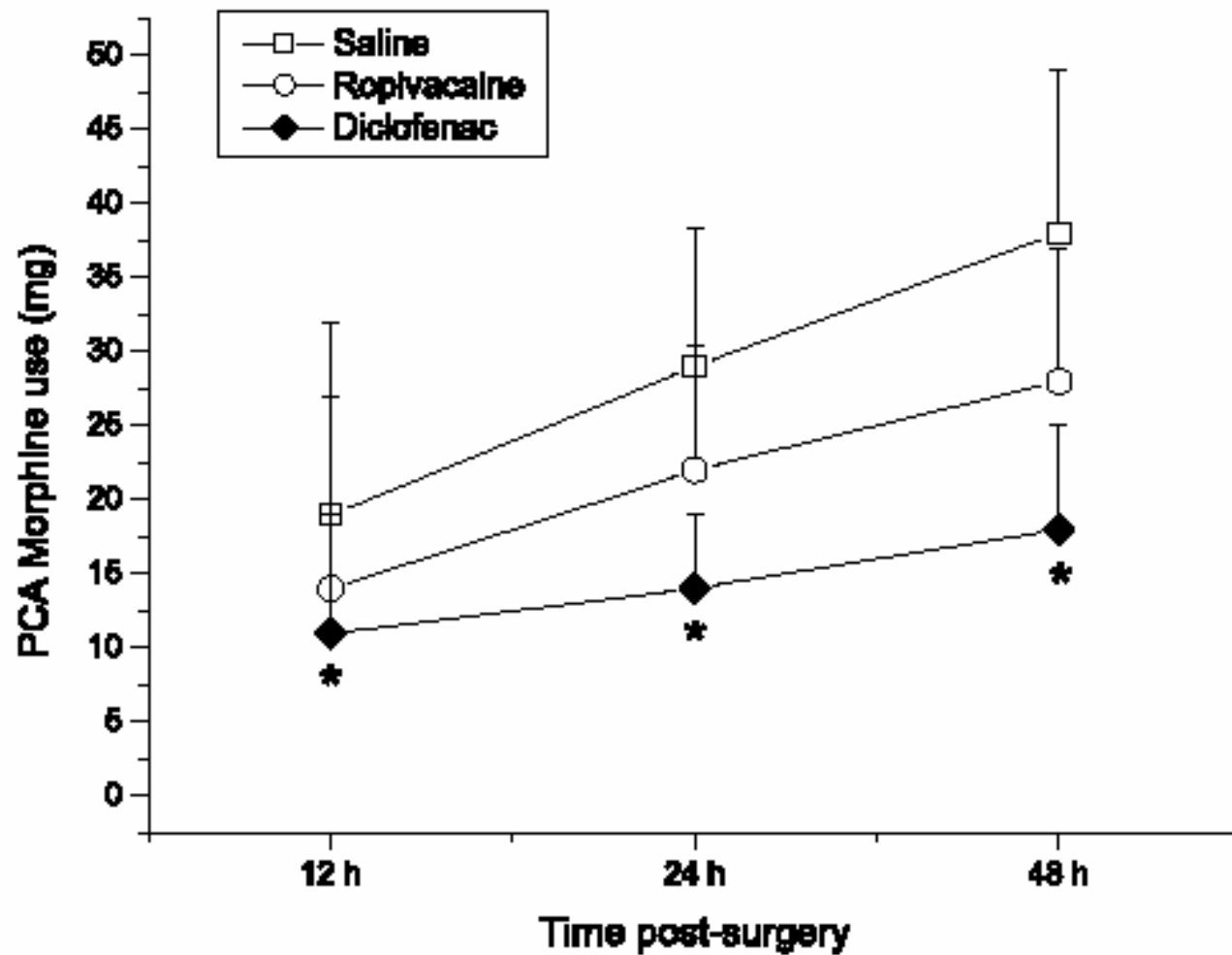
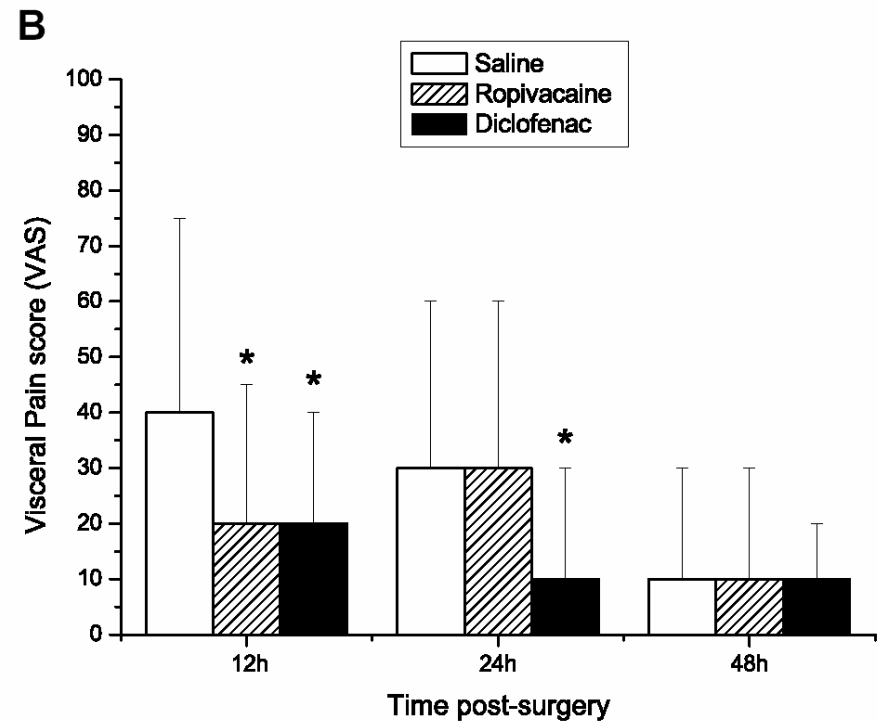
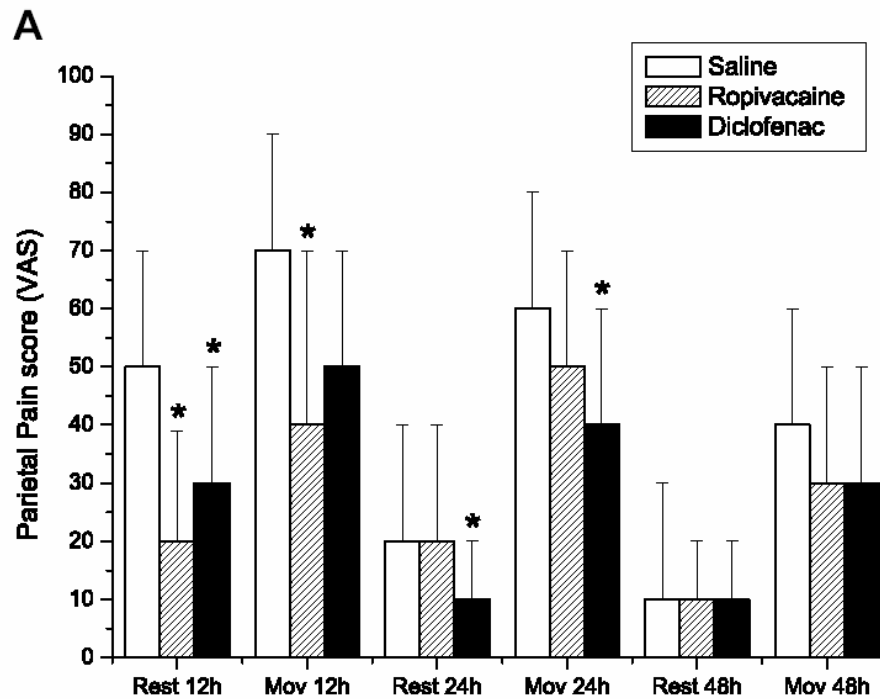


Fig. 1. Postoperative use for intravenous patient-controlled analgesia (PCA). Cumulative doses of morphine delivered by PCA device at 12, 24, and 48 h after surgery. * $P < 0.05$ with saline group. Data are expressed as mean \pm SD. Treatment groups:



Analgesics benefits of either subcutaneous ropi or diclofenac infusion on the parietal or visceral pain did not extend beyond 24 h after the surgical procedure

Residual pain at 6 months

	Group	
Residual pain at 6 months		23%

The difference was not significant



Conclusions

- Results suggest the presence of peripheral analgesic properties of diclofenac
- No effect on persistent pain



Postoperative Analgesic and Antihyperalgesic Effects of Spinal Clonidine administered during elective Cesarean section

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- Spinal clonidine added to spinal bupivacaine and μ -opioid agonist → improvement of analgesia
- α_2 -adrenoceptor agonists also possess antihyperalgesic properties
- Hyperalgesia after tissue incision:
 - participates to postop pain
 - = clinical expression of central nervous system sensitization induced by nociceptive inputs from the surgical wound

-Severe postop pain
-Central sensitization



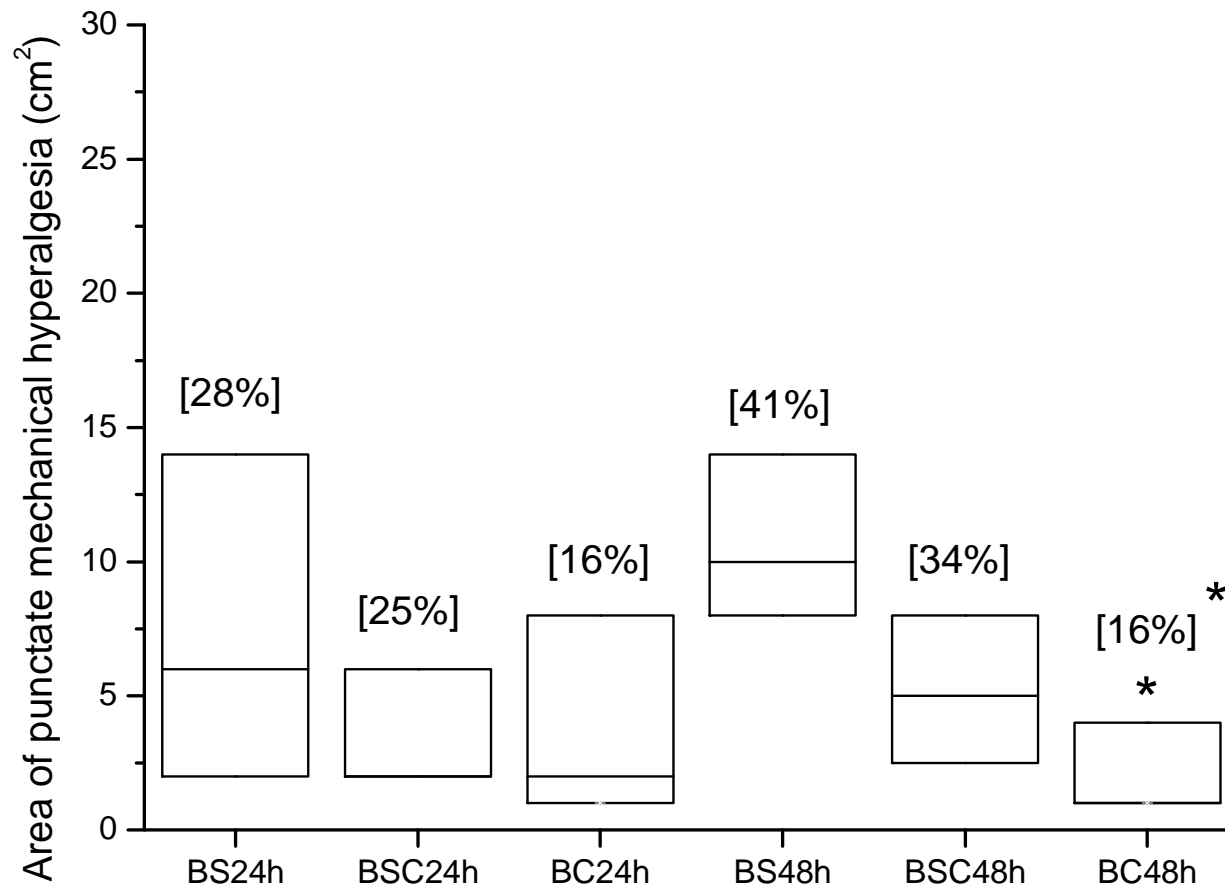
Likelihood to development of persistent pain after surgery

- 
- 0.5 % hyperbaric bupivacaine= « bupi »

	Group BS	Group BSC	Group BC
n	30	31	29
Spinal injection	Bupi Suf	Bupi Suf Clonidine 75 µg	Bupi Clonidine 150 µg

- BC, BSC used less IV morphine during the first 12 hours

F



Incidence of persistent pain

	BS	BSC	P
At 3 months	17 %		
At 6 months		12 %	3 %

The difference was not significant



Conclusions

- Spinal clonidine 150 μg reduces:
 - development
 - extent
 - incidence

} peri incisionnal mechanical hyperalgesia at 48 h after CS
- Despite its antihyperalgesic effect, this dose of clonidine displays only a short-lasting postoperative analgesia



General Conclusions

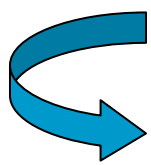
- Chronic pain after CS is a Reality:
 - 10 % → persistent pain
 - ↳ 5 % → severe pain (affecting daily activities)
- But need for further studies
 - Risk factors
 - unrelieved acute postoperative pain
 - insufficient intraoperative analgesia
- Intensified long term multimodal analgesia
- Focus attention to the immediate postpartum period (↓ acute suffering and persistent morbidity)



Future...

- Identify subjects at risk
- Develop strategies of prevention in high risk patients

Development of tools allowing to predict patient at risk (greater pain sensitivity)



*Preoperative assessments of pain responses to a nociceptive stimulation

early postoperative pain responses



*The intensity of early postoperative pain

development of chronic postoperative pain

*Genetics polymorphism:

predisposition or not to chronic pain

reaction to treatment affected or not