# Fetal Pain

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# Chapter 2

# Fetal pain

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## Introduction

The concept of fetal pain is becoming more and more relevant since the possibilities for invasive intrauterine treatment are increasing. However, there is much debate as to whether the fetus is mature enough to be able to perceive pain. But what is 'pain'? One cannot determine whether a fetus feels pain unless one has a conception of what pain is. There is a difference in opinion about what pain really *is* and that is also the difficulty in studies on fetal pain: we cannot simply ask the fetus whether or not it feels pain. We can only give indirect evidence of possible harmful effects of stressful stimuli on the developing fetus. In this review we will first explore the meaning of 'pain'. We will then discuss the fetal anatomic, neurophysiologic and behavioural development and responses which are thought to be required to experience pain. Finally, we discuss some ethical considerations and suggestions on fetal anaesthesia.

## What is pain?

The most commonly accepted definition of pain is presented by The International Association for the Study of Pain (IASP): '*an unpleasant sensory and emotional experience associated with actual or potential damage, or described in terms of such damage…. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state,* even though we may well appreciate that *pain most often has a proximate physical cause….. Pain is always subjective. Each individual learns the application of the word through experiences relating to injury in early life'* [1]. The definition presented in the Oxford Dictionary states that pain is '*a strongly unpleasant bodily sensation such as is caused by illness or injury*' [2]. What both definitions correctly capture is the subjective nature of pain. Pain is typically something that is consciously felt: although one can be injured without being aware of it, one cannot be in pain without being conscious of it. Similarly, although one may not be injured, one can still feel pain. Pain is above all an unpleasant *feeling*. The IASP considers emotion as an essential feature of pain, where the Oxford Dictionary does not include 'emotion' as an essentiality for the experience of pain. According to the IASP there has to be an emotional reaction for the stimulus to be recognised as 'pain', this emotional reaction is subjective and has to be learnt through experiences in life. Following this line of reasoning, the fetus is arguably not capable of feeling pain, since it has not *learned* yet what 'pain' is.

There are various ways in which one can explain how 'emotion' relates to pain. The unpleasant feeling of pain itself could be regarded as an emotion. However, this cannot be the sense in which the IASP uses the term, because it would be a circular argument to say that a fetus cannot feel pain because it has no emotions. Emotion could also be viewed as distinct from pain, and this is probably the sense in which the IASP uses the term. Emotion can modulate pain, either enhance or dull the experience: it is well known that a soldier wounded in battle often feels nothing at the time and conversely people who are depressed often feel more pain than at other times. However, the fact that the suffering associated with nociceptive stimulation in adults can be affected by activity in other parts of the brain, does not prove that in a naïve being such as the fetus, there can be no experience of pain. The fact that the sensation of pain can be affected by previous experience does not preclude the conclusion that previous experience is necessary to feel pain. Such an argument would suggest that a newborn is not capable of feeling pain. The view that to experience pain it is necessary to have had experienced pain before, is self-defeating because then there could never be a first experience of pain.

The term 'nociception' is often used to describe or measure pain. It is important however, to recognize that nociception and pain are not the same. Nociception is the process whereby noxious stimuli are sensed and transmitted to the brain. While nociception only refers to the neural activity, pain refers to the unpleasant feeling. Nociception requires no level of consciousness, while pain does. Although nociception often causes pain, it is possible that nociception occurs without there being pain (for example in patients with transection of the spinal cord, in which a noxious stimulus is administered below the level of transection). Similarly, pain may also occur in the absence of nociception: a patient may complain of pain in the absence of tissue damage or another peripheral stimulus. While nociception and pain are distinct concepts, the former often causes the latter.

The fetal nervous system is different from the adult nervous system. Below we will discuss the results of anatomical, functional and behavioural studies on the fetal nervous system.

## Neuroanatomical maturation

In adults, the processing of nociceptive stimuli requires peripheral sensory receptors, afferent neural pathways and subcortical and cortical neural integration of the related impulse traffic [3]. The stressful signal is processed into a number of stress related ortho and parasympatic autonomic and hormonal reflexes and into a subconscious feeling of pain. This happens in structures like the brain stem, the basal ganglia, the amygdale and the hypothalamo-pituitary system [4-6]. The peripheral receptors, also known as the nociceptors, develop from the seventh gestational week onwards [6]. Peripheral afferents appear at 8 weeks of gestation and make synapses into the substantia gelatinosa, a part of the dorsal horn of the spinal cord [6-8]. A functional reflex circuitry develops at the same time as the peripheral afferent makes a connection with the spinal cord [6, 8]. The connection between the spinal cord and the thalamus (an obligatory station through which nearly all sensory information must pass before reaching the cortex) starts to develop from 14 weeks onwards and is finished at 20 weeks [4, 7, 9]. The thalamocortical connections are present from approximately 17 weeks of gestation. They begin to grow into the cortex at 24-26 weeks of gestation, meaning that pain impulses may reach the cerebral cortex for the first time during approximately week 26 [5]. Some investigators therefore state that a fetus therefore is able to feel pain from about 26 weeks onwards [10]. Others however, argue that thalamocortical connections are not a necessary criterion for (fetal) pain perception as clinical data show that ablation or stimulation of the thalamus alone is sufficient to alter pain perception in adults [11-14]. Moreover, pain perception during fetal and neonatal development does not necessarily involve the same structures involved in pain processing as those in adults, meaning that the lack of development of certain connections is not sufficient to support the argument that fetuses cannot feel pain until late gestation [10]. Some say even that the structures used for pain processing in the fetus are completely different from those used by adults and that many of these structures are not maintained beyond specific periods of early development [8, 15]. Although the thalamocortical connections are not complete before the end of the second trimester, other pathways are present in the developing nervous system. The fetus might not be able to perceive pain at a cortical level; however he might be able to perceive painful stimuli, process the information and alter the development of the nervous system as a response to pain [16]. It seems, however, that there needs to be at least some cortical function to be able to perceive pain as such, which means that the very young fetus is probably not capable of

feeling pain [17]. Noteworthy, the serotonin-releasing inhibitory descending pain fibers only develop after birth. It is therefore safe to assume that if the fetus feels pain, it even feels more pain than the infant or adult [18].

### Neurophysiological data

The presence of anatomical structures alone is insufficient to demonstrate a capacity to feel pain. The structures need to function as well. Functionality of anatomical pathways can be measured indirectly through electroencephalography. An electroencephalogram (EEG) unfortunately provides no direct evidence of the capacity to feel pain, but merely provides data about the functional capacity that is *required* for experiencing pain. It can reflect on the function of subcortical and cortical structures and it can determine the presence of cerebral dysfunction and distinguish the waking from the sleeping state. There are no 'pain patterns' discernable on an EEG, so one cannot determine whether someone is in pain by looking at the EEG recordings. A primitive EEG is present from 20 weeks of gestation [4, 5] More advanced recordings show sleep-wake patterns by 24-30 weeks of gestation [19]. Particularly important is the ascertainment that the fetus shows sleep-wake patterns, because wakefulness or rather consciousness is considered to be crucial for the feeling of pain. Wakefulness and consciousness are not the same: wakefulness (and sleep) is a state of brainstem and thalamic activity whereas consciousness is a function of the cortex. In order to be conscious, all incoming information must be available to all parts of the cortex at the same time. Sleep is an arousable state of unconsciousness. Thus, it is possible to be awake and not conscious (as in some persistent vegetative states, where a wakeful EEG pattern can be present in an unconscious patient) and to be awake and conscious, but not to be asleep and conscious. Pain is most directly linked rather to consciousness than to wakefulness. As the EEG measures only wakefulness and not consciousness the relevance of this measure could be questioned. However, as stated above, it seems reasonable to assume that consciousness does not exist without wakefulness. Therefore, if wakefulness is established in the fetus, consciousness (and hence pain) could also be possible. Some argue that by late gestation 95% of fetal EEG activity consists of fetal sleep and the remaining 5% represents transition phases between sleep states [20]. This would imply that the fetus is never awake and therefore not able to feel pain. This view is supported by the fact

that, unlike in a newborn, a chronic threatening noxious stimulus in a fetus will not lead to full arousal but on the contrary will lead to cessation of fetal movements and redistribution of cardiac output away from peripheral organs to key central organs such as the fetal brain. We will discuss this further below. These data seem to demonstrate that stimuli which induce arousal to waking postnatally do the opposite in utero; they further suppress fetal arousal as arousal would further reduce limited fetal energy resources without any advantage [20]. However, fetal EEG patterns for wakefulness and sleep are presumed to be quite different from those of the adult, making interpretation of the signal difficult. Perhaps the fetal EEG recordings indicate that the fetus does not have similar states of wakefulness as an adult, but they cannot prove that the fetus does not have the sort of wakefulness necessary for consciousness and pain [17]. However, EEG data alone do not provide sufficient evidence of fetal pain. Alternative indirect approaches are needed to assess the presence of nociception and pain in the fetus.

### Hormonal and hemodynamic changes

Fetuses show a significant alteration in stress hormone levels and associated hemodynamics following a noxious stimulus, indicating that there is at least stress and perhaps even pain. Interpretation of these changes is however complicated because these changes are relatively unspecific indicators of subjective painfulness, even in adult patients.

Cortisol, beta-endorphin and noradrenalin are hormones that are released in response to a noxious stimulus, in order to minimise pain. Cortisol acts as an anti-inflammatory agent and beta-endorphin and noradrenalin act to dampen the painful feeling. These hormones rise in response to a painful stimulus and increasing levels of these hormones mean that the pain is alleviated. After invasive intrauterine procedures which involved transgression of the fetal abdomen, Giannakoulopoulos et al. described a significant rise in the stress hormones cortisol, noradrenalin and beta-endorphin [21, 22], which was independent of the level of stress hormones in the mother [23, 24]. This rise was not present in intrauterine procedures in which no noxious stimulus was applied to the fetus. The authors caution in their article that a hormonal response cannot be equated with the perception of pain: these findings do not definitively provide evidence for fetal pain. However, we agree with their conclusion that their

study: 'shows that as with neonates, the fetus mounts a similar hormonal response to that which would be mounted by older children and adults to stimuli that they would find painful' [21]. Some argue that since the increases in stress hormones were much smaller than those usually seen in adults, there is no evidence that the fetus is capable of feeling pain [25, 26]. It seems, however, more reasonable to assume that the fetus has merely an underdeveloped capacity for reacting to the feeling of pain and not an absent sense of pain. Noteworthy, from adult studies it is known that postoperative high cortisol levels are associated with *lower* pain ratings [25]. This does not mean that high cortisol levels are not associated with pain, but can be explained by the fact that, as described before, stress hormone levels *rise* in the presence of pain, but the increase of the hormones is associated with relief of pain.

Teixeira et al. has shown that in response to invasive procedures the fetus mounts a hemodynamic response [27]. The middle cerebral artery pulsatility index value has been described to decrease after intrauterine transfusions in the intrahepatic vein (in which a noxious stimulus is given) and not after transfusion in the placental cord insertion (in which no noxious stimulus is given). The decrease in pulsatility index is consistent with the phenomenon of brain-sparing, by which blood is redistributed to the most crucial organs, i.e. the brain and heart. However, in a recent study performed in our centre, we measured a decrease pulsatility index in both groups following transfusion for fetal anaemia, which might indicate that this difference is less likely to be due to stress or pain, at least in anaemic fetuses. We hypothesised that the changes were most likely related to the volume load [28].

### Fetal behavioural and stress responses

Behaviour integrates many functional systems and is usually interpreted as the expression of a particular mental state. Therefore, it is logical that several authors attempted to establish pain through behaviour. The fetus is capable of spontaneous movements and increasingly complex responses from early in gestation [29, 30]. Following a noxious stimulus, fetuses can exhibit a withdrawal reflex. It is difficult to classify this reaction as pain, because it is known that in term neonates the same reflex is activated with a threshold much lower than that which would produce discomfort in a child or adult [31]. It is known that the reactions of preterm infants to pain can be diffuse, non-localised and sometimes completely absent [32, 33]. This

inconsistent reaction may reflect the immaturity of the developing nervous system and given these inconsistencies, any attempt to quantify pain responses in neonates, or fetuses for that matter, using behavioural measurements is extremely difficult. Opponents of the concept that fetal pain exists might say that behavioural changes are always contributable to mere reflexes and that these changes do not reflect any unpleasant mental state. However, these behavioural changes are probably the best insight we can currently get into the fetal and neonatal mind. We cannot expect greater behavioural responses from these children and it seems unfair to presume that fetuses cannot feel pain merely because they do not yet have the ability to express themselves more clearly. It is, of course, a fact that reflexive movements do not imply pain. Spinal reflexes, for instance, can result in withdrawal of a limb from the painful stimulus even before this stimulus reaches the cortex. However, reflex movements do not preclude pain. Distinguishing between reflexive behaviour following a non-painful event and reflexive behaviour following a painful event can be very difficult. We can only try to correlate the reflexive behaviour to the anatomical and functional evidence for fetal pain we have considered above. Looking at these three phenomena combined, it seems reasonable to assume that the reflexive behaviour that the fetus exhibits following a noxious stimulus, indeed implies pain or stress.

## Short term consequences of fetal pain

The newborn central nervous system is capable of mounting a chronic pain response to painful stimuli, which means that neonatal repeated exposure to painful stimuli can result in hypersensitivity for further stimulation [34]. This hypersensitivity can be measured with von Frey hairs, by determining the flexion reflex threshold. The cutaneous withdrawal reflex occurs when a limb is withdrawn in response to a painful stimulus of sufficient magnitude and the threshold for occurrence of this reflex is reported to decrease after repeated exposure to the stimulus. This indicates a hypersensitivity to tissue damage analogous to tenderness or hyperalgesia reported in adults [34]. Treatment of the damaged area with topical anaesthetic cream was found to reverse this hypersensitivity. Repeated exposure to painful stimuli is also associated with behavioural immaturity: difference in response to a painful event between infants of different postnatal ages can be seen as early as 32 weeks' postconceptual age [35]. Earlier-born infants showed decreased behavioural response (less facial eye

squeeze, less nasolabial furrow, higher heart rate) following a painful stimulus as compared to newly born infants with the same postconceptual age. This behavioural immaturity was associated with a greater frequency of invasive procedures in the earlier-born infants [35]. Infants treated in a neonatal intensive care unit for 4 weeks showed decreased behaviour and increased cardiovascular response to the pain of the heel prick. The responses correlated with the number of invasive procedures experienced after birth [35]. Using the Neonatal Facial Coding System the preterm neonatal response to painful stimuli was also measured [36]. Neonates were observed during a heel lancing procedure and were found to exhibit a distinct set of facial movements that are also characteristic for term infants and adults subject to painful stimuli. Interestingly, the facial movements varied depending on whether the infant was asleep or awake at the time of the lancing. This underlines the notion that wakefulness facilitates the experience of pain, as described above.
In infants undergoing abdominal surgery post-operative wound hypersensitivity was observed [37]. In the wound area, hypersensitivity was observed as well as a significant fall in the sensory reflex threshold.

As described before, the fetus shows, similar to the neonate, circulatory and hormonal changes in reaction to a painful stimulus. It is not known if the threshold for these changes decreases after repeated exposure or if it will lead to hypersensitivity to further stimulation.

### Long term consequences of fetal pain

Some presumably painful fetal conditions can lead to long term changes in infant sensitivity. The abdominal skin reflex was used to evaluate abdominal sensitivity of infants with prenatally diagnosed unilateral hydronephrosis. The abdominal skin reflex threshold on the affected side was significantly lower than on the unaffected side and this persisted for at least three months after corrective surgery [38]. As post-conceptual age increases, an increase of the abdominal skin reflex threshold would be expected (as the capacity of the neonate to distinguish between painful and painless stimuli is maturing). However, in infants with unilateral hydronephrosis this increase did not occur, even on the unaffected side of the abdomen. This suggests that exposure to noxious stimuli in fetal life somehow disrupts the normal nociceptive development

resulting in changes that are still present several months after birth and even after corrective surgery.

In infants, circumcision without anaesthesia can cause behavioural changes that persist long after the expected duration of pain. It has been observed that circumcised infants show a significantly stronger pain response to routine vaccination at 4-6 months of age than uncircumcised infants [39]. A study done in a rat model shows that at the site of a wound in the neonatal period there can be long lasting sensory nerve sprouting, which may explain the hypersensitivity to pain [40]. Studies in rat pups as well as human fetuses show a permanent spinal cord level sensitisation as an effect of repetitive painful stimuli [41]. After repetitive stimulation, the synaptic connections in the spinal cord show lower thresholds for excitation [42]. Long-term follow-up studies have shown a correlation between prolonged stay in neonatal intensive care unit and altered pain thresholds and abnormal pain-related behaviour in later childhood [43].

All these data suggest that early neonatal exposure to a painful stimulus causes long-lasting changes in the normal pain development [44-47]. We know that pain itself is not remembered [48], but the painful event can be incorporated in the implicit memory, that operates at the level of conditioning, leading to altered or disturbed pain behaviour [49]. Whether or not fetal exposure to pain results in similar long-lasting changes remains uncertain but seems probable, as noxious stimulation might not need to penetrate consciousness to substantially alter the course of sensory development [50]. The final shaping of the brain circuitries depends predominantly on endogenous and sensory-driven neural activity [51]. It is possible that a harmful external stimulus somehow disrupts the patterns of neural activity leading to an abnormal brain development [52].

## Ethical considerations

If a fetus is indeed capable of experiencing pain, this would have consequences for how we approach the fetus, especially in case of termination of pregnancy, fetal surgery and fetal malformations. The US federal government is considering legislation that will require doctors to inform women seeking abortions that 'there is substantial evidence that the process of being killed in an abortion will cause the unborn child pain'. The proposed bill mandates that a fetus of more than 22 weeks' gestational age should receive pain-reducing drugs before abortion [53-55]. There is a political debate on the issue of fetal pain with radical proponents and opponents [56-58]. If a woman can be persuaded that an abortion will cause pain to her fetus, she might decide against having one. And if society can be convinced that fetuses feel pain, it might be easier to pass restrictions against abortions. If there would be convincing evidence that a fetus is unable to feel pain, this could play a role for some women in the decision-making on termination, and take away one argument of pro-life supporters. These political issues cloud the discussion about the existence of fetal pain.

There is a lack of studies on pain in fetuses undergoing surgery or fetuses with possibly painful congenital malformations such as hydronephrosis or hydrocephaly, gastroschisis, or a fast growing tumour. Should we administer pain relieve to these fetuses as we would provide adequate analgesia to a neonate of the same postconceptual age? When considering analgesia for such chronic pain issues, there can be competing needs of the fetus and the pregnant woman. From a legal perspective, despite the lack of agreement on the moral status of the fetus, prenatal imaging technologies such as ultrasound promote the notion of two 'patients', in stead of just one, the pregnant woman [59]. Part of the difficulty is that some of the main principles of medical ethics, justice, respect for autonomy, beneficence and non-maleficence contain little capacity to balance the sometimes competing needs of patients. As the fetus is recognised more and more as a patient, the status of the pregnant woman seems to alter as she tends to become less visible during discussions about fetal surgery [60]. For clinicians it remains important to consider the wellbeing of both patients when considering for instance fetal surgery and fetal anaesthesia. The shift towards recognising the fetus as a patient has also lead to the assumption that the fetus might be able to experience pain. As described above, some authors have demonstrated a stress response in fetuses following a noxious stimulus [21]. Others

however believe that this response cannot be equated with pain [61]. Some argue that in the absence of consensus one should assume that fetal pain exists until proven otherwise and act accordingly [62]. Others believe that this might lead to unnecessary procedures to provide analgesia and potentially increase distress for pregnant women undergoing these procedures. Due to all these controversies there is currently clearly a lack of agreement whether or when fetal pain might need to be considered and hence whether or when fetal anaesthesia might need to be considered.

## Fetal analgesia: indications and methods

In both children and adults, several studies have shown the association between inadequate anaesthesia, a large stress response and poor post-operative outcome [63-65]. There is some evidence suggesting that the same is true for the fetus [66, 67]. It is currently unclear what level of suppression of the stress response is optimal in terms of outcome. For instance, the stress a fetus experiences during normal vaginal delivery is assumed to be beneficial to the child's respiratory adaptation to the external world and not harmful at all. However, given the evidence that stress responses may have long term consequences, we should consider severe fetal stress or pain as a realistic problem. When considering performing invasive intrauterine treatment it seems prudent to provide adequate anaesthesia to both mother and fetus. Besides the argument of achieving adequate fetal anaesthesia, there are other purposes that justify the administration of drugs: inhibiting fetal movement during a procedure and achieving uterine relaxation to improve access to the fetus and prevent contractions and placental separation [15, 68-73]. Some of the commonly used drugs, like opioids, have effects that are analgesic, muscle-relaxing and tocolytic. However, we should address the subject of fetal anaesthesia carefully as for instance opioids may alter long term responses to painful stimuli. For example, early opioid exposure has been suggested to increase subsequent responses to painful stimuli [74]. There is also concern about self-destructive behaviour in adolescence, following fetal exposure to opioids [75]. So we need to be careful not to replace the problem of no anesthesia by one with too much anaesthesia, for this might prove to do more harm than good.

In administering analgesics to the fetus, there are several options: indirectly, via the mother and across the placenta; or directly, either intravenous, intramuscular or intra-amniotic. When general anaesthesia is considered the best option for the mother, like

in open fetal surgery, the fetus will receive the inhalational agent given to the mother through placental passage. As animal data suggests, fetuses require lower concentrations to achieve anaesthesia compared to adults, and this is considered to be sufficient to provide adequate fetal anaesthesia [76]. For minimally invasive fetoscopic procedures (using needles or endoscopy to access the fetus), it is not necessary to use general anaesthesia for the mother. In these cases, the administration of safe and effective analgesia to the fetus is more challenging. Maternal administration of opioids such as fentanyl usually produces very low fetal levels, which implicates that a high maternal dose is needed for adequate fetal anaesthesia [66]. Fisk et al. report the use of fentanyl administered intravenously to the mother which then reaches the fetus through transplacental passage, or directly injecting it into the fetal circulation [65]. Administration of fentanyl intravenously to the fetus has been reported to blunt the stress response and halve the beta-endorphin and cortisol response [65]. Remifentanil is a new short acting potent opioid. It can be administered intravenously to the mother and then reaches the fetus through the placenta. Remifentanil crosses the placenta quickly and almost completely, which makes it an excellent candidate for fetal anaesthesia [77, 78].

Direct fetal intramuscular administration is associated with lower risk than fetal intravenous injection. Drawback of intramuscular administration is the prolongation of the procedure in order to await absorption. Intra-amniotic injection of analgesics could be another method to achieve fetal anaesthesia. Intra-amniotic injection of sufentanil has been described in animal models [75]. This results in subtherapeutic levels in the fetus [79]. Sufentanil is a highly lipid soluble resulting in excellent transmembranous absorption in the fetus, and it crosses the placental barrier less then fentanyl, thereby protecting the mother. Injecting analgesics intra-amniotically seems to result in longer lasting (sub) therapeutic levels of the medication in the fetus.
Regional anaesthesia, such as epidural anaesthesia, does not anesthetise the fetus [80]. In some situations, however, regional anaesthesia can be beneficial to the mother.

## Summary and conclusion, directions for future research

Neuroanatomical, neurophysiological, hormonal, hemodynamic and behavioural data indicate that a fetus is capable of reacting to noxious stimuli, implying that the fetus can experience stress and possibly even pain. Long-term studies show that repeated exposure to painful stimuli in the neonatal period can have adverse effects on the development of the neural system. The changes described can be long-lasting, perhaps even life-long. Data on the effects of noxious stimuli on the fetus are sparse; it seems plausible, though, that long term consequences are similar for fetuses and neonates of the same postconceptual age. We therefore think that when performing invasive intrauterine procedures, it is important to accomplish fetal anaesthesia to protect the fetus from possible harmful effects on the developing neural system. It is difficult to determine from what gestation onwards fetal anaesthesia should be provided; however, we feel that it should be considered from at least mid-gestation. The studies on fetal pain published thus far have not been able to define what pain really *is* and what the significance is of the changes measured in a fetus following a painful stimulus. We don't know from what gestation onwards fetal analgesia is absolutely necessary, which anesthetic to choose and what the long-term consequences are of (repeated) fetal exposure to a painful stimulus. Future research should focus on these aspects. Only when we can demonstrate that the neural system is damaged, disrupted or somehow altered after fetal exposure to (repeated) painful stimuli, physicians can be convinced that it is necessary to provide adequate fetal anaesthesia during invasive intrauterine procedures.

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