

Motherhood and Memory: A Review

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Psychoneuroendocrinology (2001) **26**: 339-362

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Running title: Motherhood and memory

Summary

This paper reviews the literature on intellectual change during and following pregnancy in humans. Whilst much has been written in an impressionistic way, this area has received little serious scientific attention, and at the beginning of the twenty first century considerable gaps in our knowledge remain. Targets for future research are suggested. The second part of the paper reviews the complex hormonal changes that place during pregnancy and birth and examines the impact that these changes may have on cognition, drawing together the findings from a number of scientific fields. Whilst this review may generate more questions than it answers, we hope that it will create interest and stimulate research in this long neglected field.

Keywords: memory, pregnancy, childbirth, hippocampus, estrogen, progesterone.

Introduction

British media interest in intellectual decline during pregnancy soared spectacularly following the report of Holdcroft et al's study in the *New Scientist* (Moore, 1997). Widely misreported and misunderstood, this study, which did not report psychometric findings or employ any subjective measures of memory function, actually demonstrated an increase in brain volume following delivery. It nevertheless generated headlines such as "She's pregnant and her brain is shrivelling" and "Baby...is eating my brain cells". The British tabloids had a field-day; "All stomach & no brain" and "My brain hurts...but it's only little" formed just some of the attention-grabbing copy. As would be expected, few of the articles addressed themselves to the data from Holdcroft's study but the idea that "pregnancy shrinks your brain" clearly hit a resonant chord with a number of (mostly) female journalists who provided an abundance of anecdotal evidence. In all, the message from the press coverage was clear; "scientists have proved what mothers (and midwives) have known all along". "Porridge Brain syndrome" has been long recognised in midwifery folklore and there have been calls for the formal preparation of prospective mothers for their impending "brain drain" in the same way that they are forewarned about the "baby blues" (Burgoyne, 1994; Parsons & Redman, 1991).

'Maternal Amnesia': A review of the evidence for cognitive change associated with pregnancy & childbirth.

Despite this febrile media frenzy, memory disturbance associated with pregnancy and childbirth has received little attention from neuropsychologists and as yet there are few well-controlled longitudinal studies of the intellectual changes that may occur during and following pregnancy. In the following sections we review the evidence for subjective and objective cognitive impairment during pregnancy.

Subjective cognitive impairment during pregnancy

In an early review of the psychological changes associated with normal parturition Robin (1962) noted the 'absence of serious special investigation of pregnancy' although he found that 'much had been written in an impressionistic way'. Nearly four decades later, we found a similar picture. A number of anecdotal reports written by professional women can be found in the modern literature (Baildam, 1991; Burgoyne, 1994; Welch, 1991). In a personal account of her experiences with a new baby, Baildam (1991), reports that her mental activity was 'well below par' on her return to her post as a senior resident physician at the end of four months of maternity leave. She goes on to assert that 'the maternal amnesia syndrome is a reality which most mothers are too frightened to admit to anyone, and yet will talk of with obvious relief when they realize it is common, normal and temporary'. In a similar vein, Burgoyne (1994) describes 'a catastrophic deterioration of neuronal function.... (that) started early in pregnancy'. She describes difficulties in

concentration and a marked deterioration in expressive language skills. These problems apparently progressed throughout the pregnancy .

Similar cognitive difficulties are also reported in a number of more systematic studies that have examined the subjective experience of cognitive change during and after pregnancy. In one of the very first studies in this field, Jarrahi-Zedah et al (1969) found that 12% of their sample of pregnant women complained of 'mental foginess' during the pregnancy. This increased to 16% of the sample postpartum and was found in one third of multiparous women. In a more recent study, Poser (1986) surveyed 67 pregnancies in 51 professional women. The subjects were asked to fill out a questionnaire covering a number of physical and neuropsychological complaints. Over 80% of the sample reported increased forgetfulness, with 38% reporting that this was their only symptom. Reading difficulties were also common with more than half of the women reporting problems. Confusion, disorientation and poor concentration were also recorded. Like the individual reports of personal experience, the authors of this study provide rich anecdotal descriptions of the experience of pregnant women, for example quoting one neurologist who reported that 'In the most general terms I felt incredibly stupid...my thought processes seemed to move along with the speed of cold sludge ... I felt almost as though I had a bradykinetic brain'.

In a retrospective study, Parsons & Redman (1991) collected questionnaire data from 236 primiparous women. The women completed the questionnaire within three days of giving birth and were asked to rate the frequency of the problems they experienced during the final three months of pregnancy in three cognitive domains (concentration, remembering things,

absent-mindedness). More than half of the sample reported that they had experienced a deterioration of function in one or more of these areas. Although the extent of the deterioration was not addressed, the authors found that women who reported a more global deterioration of function were older, tended to be married and had a higher level of education than those who only reported problems in one specific area.

In a second study reported in the same paper, the authors interviewed fifty multigravid women during various stages of their pregnancies. Eighty-two percent of the sample reported changes in cognition associated with pregnancy with two thirds citing memory disturbance as the biggest problem. Most of the affected women noticed that the onset of the changes occurred during the second or third month of gestation. In addition to these cognitive changes one third of the women also reported poor coordination resulting in significantly more accidents around the home (dropping/spilling things, minor burns etc.) during their pregnancies. In a more recent study, Janes et al (1999) found that primigravid and primiparous groups reported overall poorer memory performance since pregnancy relative to controls. The groups did not differ on self rated levels of physical or emotional health, or anxiety level. A number of other studies have confirmed these findings with a variety of more or less sophisticated techniques (Brindle et al., 1991; Sharp et al., 1993). With few exceptions the studies that have examined subjective reports of cognitive change during pregnancy suggest that a substantial proportion of women experience some degree of disturbance in cognitive ability with estimates ranging from 50% to 80%. Whilst sampling bias is undoubtedly a strong factor, there is a hint in a number of studies that professional women and those with higher education may experience a greater degree of decline

(Baildam, 1991; Burgoyne, 1994; Parsons & Redman, 1991; Welch, 1991). Forgetfulness and 'a poor memory' appear to head the list of difficulties across these studies, but the problems identified are by no means limited to the memory domain. Distractibility, weak concentration, word finding difficulties, poor co-ordination and general cognitive slowing are all reported.

Although the studies cited have suggested that subjective memory complaints are a significant feature of pregnancy for many women, subjective reports are not always a reliable guide to the extent of memory impairment evident on objective testing. In everyday terms, a number of cognitive failures are generally attributed to 'a poor memory'. However more detailed neuropsychological investigations and interviews often reveal deficits in concentration, attention, perception and even sensory disturbance that may underlie the behavioural disturbance perceived as memory failure. In addition, complaints of 'memory difficulties' may simply reflect an overall deterioration in cognitive function. This may be masked if memory functions are the only abilities addressed.

The relationship between subjective and objective memory impairment appears to vary in different patient populations. Sunderland et al (1983) found significant correlations between subjective memory complaints and psychometric measures, particularly paragraph recall, in head injured patients. However complaints of poor memory in depressed patients may far exceed measured impairment (Reifler et al, 1982). In a sample of temporal lobe epilepsy patients, Vermeulen et al (1993) found that subjective memory complaints bore little relation to objective measures and were more closely associated with levels of anxiety, depression

and other psychosocial factors. Irritability, mood swings and increased lability of mood during and after pregnancy have been reported at similar rates to the cognitive changes (Jarrahi-Zadeh et al. 1969) and pregnancy and childbirth have long been recognised as very stressful events in both physical and psychological terms. The deleterious effects of chronic and acute stress on cognitive performance are well documented (Buckelow & Hannay 1986; King et al, 1978 ; Mueller, 1979), as are the cognitive deficits commonly associated with anxiety and depression (Veiel, 1997). It is possible therefore that the common complaints of cognitive decline during pregnancy simply reflect the effect of increased levels of both psychological and physical stress. This whilst the groups in Janes et al (1999) study did not differ on self rated levels of physical or emotional health, or anxiety level, sleep disruption was a significant predictor of the level of subjective memory complaints. They concluded that self reports of memory change during pregnancy and postpartum were related to life changes such as changes in sleep pattern and that memory complaints probably reflected changed perceptions rather than objective changes.

Objective Cognitive Impairment in Pregnancy

Although a number of studies have examined memory for a discrete event in peripartal women, most commonly childbirth, (Niven & Brodie, 1996; Pesce, 1987; Simkin, 1992) few have employed standardised neuropsychological tests to quantify general memory abilities and until recently, there have been no well designed longitudinal studies that have examined the relationship between subjective memory complaints, psychological state indices and objective measures of cognitive function (but see Keenan et al. 1998).

Memory skills are conceptualised as a distinct set of abilities that dissociate from other cognitive domains such as intelligence, perception and language abilities. However within this broad categorisation memory comprises not a single system but an alliance of interrelated subsystems (Baddeley et al, 1995). Short-term versus long-term memory distinctions have now been abandoned in favour of the concepts of working memory and implicit/explicit memory. Working memory can be defined as the capacity to perform tasks that involve simultaneously storing and manipulating information. Implicit (or non declarative) memory, can be preserved in classic amnesic patients and includes the learning of skills and habits, priming, classical conditioning and non associative learning. Explicit (or declarative) memory includes memory for facts (semantic memory) and memory for events (episodic memory). Objective memory tests are usually designed to test a particular aspect of memory and may focus on the acquisition, consolidation and retrieval of information within a particular subsystem. It is therefore very important to carefully examine the type of memory test employed in a study if one is to draw reasonable conclusions regarding the organic basis of any deficits.

Implicit (non declarative) Memory

Brindle et al (1991) examined both memory complaints and objective performance in a sample of 32 pregnant women. Two thirds of the pregnant sample reported memory difficulties compared to only one in ten of the controls. The perceived memory deficit during pregnancy was most marked for primigravid subjects and appeared to be particularly

marked in the second trimester. The self-rating measures were significantly correlated with performance on a priming task. Priming scores were also *positively* correlated with measures of anxiety i.e., the more anxious subjects performed better on the task than those who reported low levels of anxiety. This interesting finding is discussed further in the final section. Although poor priming was associated with below normal rating of memory during pregnancy, no significant differences between the pregnant women and the control group were found on formal measures of recall and recognition. The relationship between scores on these tests and the subjective memory complaints or the anxiety ratings are not reported. The authors note that deficits in implicit, rather than explicit learning processes may account for many of the everyday memory difficulties reported by pregnant women.

Implicit memory skills have also been examined in animal studies. Kinsley et al (1999) examined the performance of three groups of rats in a dry land version of the Morris water maze. They found that maternal rats, and rats that were foster-mothers took significantly less time than nulliparous rats to find and locate food. They argue that the neural activity brought about by pregnancy and the presence of pups may literally reshape the brain fashioning a more complex organ than can accommodate an increasingly demanding environment.

However the fact that the foster mothers were as fast as the natural parents suggest that pregnancy and the attendant hormonal changes were not a significant factor in the improved performance. It is possible that the presence of pups for both the maternal and foster-rats increased their anxiety/hunger levels and thus improved their performance.

Explicit (Declarative) Memory

Silber et al (1990) examined the peripartal performance of 20 women who were tested using computerised measures of memory and attention on five occasions; the first towards the end of their pregnancy and the last, one year postpartum. Twenty non-pregnant controls were tested at similar intervals. The authors found that the pregnant women improved their performance on a verbal learning task significantly more than the controls when their results at 6 and 12 months after delivery were compared with those from the end of their pregnancy and up to three months post-partum. No baseline data were available for the pregnant group prior to their pregnancy and the authors did not compare absolute levels of function between the two groups at each stage.

Many of these methodological shortcomings have been addressed in another recent study that created a large amount of media interest when first presented at the Society for Neurosciences conference in 1997 (Keenan et al. 1997; 1998). Keenan and her colleagues examined explicit memory in pregnant women and closely matched controls in a longitudinal study design, testing the women during each trimester and again 3 months post delivery using standardised neuropsychological tests. Levels of depression and anxiety were also monitored throughout the period of the study. The study demonstrated a significant decline on the story recall task in the pregnant women from the second to third trimester. Although the pregnant group were significantly more depressed and anxious than the controls, this did not appear to be related to the cognitive changes. The memory deficits recorded during the third trimester were not evident 3 months following delivery and the pregnant group performed at levels comparable to the control group on all tasks at the end of the study. The

authors conclude that there is a significant decline in declarative memory during the third trimester of pregnancy, not attributable to depression, anxiety, sleep deprivation or other physical changes; these deficits appear to have resolved by three months after delivery.

Sharp et al (1993) also found deficits in explicit memory skills. Their pregnant women were significantly impaired in the recall of lists of words compared to a matched control group. As in the previous study the deficit was particularly marked on tasks where learning was incidental rather than explicit. No significant deficits were found on measures of recognition memory. Although self-ratings of both anxiety and memory problems were obtained, these were not analysed in relation to performance on the formal memory tests administered.

In a well designed study, Eidelman et al (1993) used standardised neuropsychological tests to compare the cognitive performance of one hundred women in the days following delivery of healthy full term babies, with that of their male partners, non-pregnant childless women and hospitalised women in the third trimester of pregnancy. Their results suggest that parturients had a significant deficits in verbal and visual recall on the first day post-partum, but that these deficits were transient and no longer apparent two to three days after delivery. The administration of analgesia during labour did not exacerbate the cognitive deficit. The authors suggest that their results indicate that the observed cognitive deficit is not a side effect of intra-partum medication but rather due to the stress and exhaustion that results from labour and delivery.

The status of the 'maternal amnesia' syndrome

This review has highlighted many important unanswered questions in this field. Although there have been calls to recognise 'maternal amnesia' (Baildam, 1991) or 'benign encephalopathy of pregnancy' (Poser et al. 1986) as a syndrome, there is as yet, no clear picture of the core symptoms. Whilst the studies that have examined subjective complaints appear to emphasise memory skills, deficits in attention, concentration, coordination and general cognitive slowing are also commonly reported. There is conflicting evidence regarding the impact of pregnancy on implicit memory skills. Although there is some convergent evidence to suggest that learning and recall may be compromised during pregnancy, the use of standardised neuropsychological tests in a design that controls for psychosocial variables is rare. In addition, a wide variety of tests are rarely administered and thus it frequently not possible to comment on the specificity of the deficits reported in the context of other cognitive abilities. In order to ensure the specificity of a particular type of memory deficit, one must measure other cognitive spheres and show that on these measures the subject scores within normal limits. However the important study by Keenan et al suggest that neuropsychological tests, with an emphasis on explicit memory skills are sensitive to memory complaints experienced in during the third trimester at least. In addition, although widely held to be transient, the typical duration of cognitive disturbance varies significantly, with some studies reporting resolution within 2 days post-partum (Eidelman et al, 1993) and others finding continued disturbance three months (Silber et al, 1990) or even longer (Poser et al., 1986) after delivery. Although the cognitive disturbance is frequently attributed to the physical and emotional stresses associated with an impending birth, at least one study has failed to find support for this view (Keenan et al. 1998) emphasizing a

possible organic basis for the disturbance, with memory difficulties as the possible consequence of hormonal changes and/or other physical processes association with pregnancy that may affect neuropsychological function. Thus, whilst apparently common, the cause, nature and course of 'maternal amnesia' remain uncertain.

We have recently encountered two cases in clinical practice that have prompted us to investigate the possibility of a more rare occurrence; long term, and possibly irreversible memory disturbance following pregnancy and childbirth. In the second part of the paper we discuss these two cases and examine the endocrinological changes that occur during pregnancy and their relationship to memory function.

Case I.

Case I was a 29 year old science graduate who worked as a hospital administrator. She complained that her 'brain has gone' since the birth of her daughter, 9 months prior to the assessment. During the interview she described how she was unable to maintain her train of thought during conversations both at work and at home and was only able to take in written material if she used active-study techniques. She relied heavily on notebooks and diaries to organise both her work and domestic commitments and reported that her colleagues at work and her husband frequently noticed and commented on her memory lapses. Her pregnancy was uneventful and the birth was a vaginal delivery without complication. Formal neuropsychological testing revealed a significant discrepancy between her intellectual skills and memory functioning. On the WAIS-R, she was assessed to function in the high average range with an IQ of 116. On the Adult Memory and Information Processing Battery, she performed at a level consistent with her overall level of function on the list learning task. However on the story recall task and on tests of non verbal learning and recall her scores fell in the below average range, some fifty percentile points lower than her IQ. Thus whilst her performance was by no means clinically impaired, her scores on the memory tests suggested *relatively* poor learning and recall of visual material and weak initial registration of verbal material and one would have predicted significantly higher scores given her level of intellectual skills and educational and occupational achievements.

Case II

Case II was 44 year old mother of 4 who trained and worked as a dentist prior to the birth of her first child. Her memory problems began immediately following the birth of her first child and she visited her GP shortly after the birth to ask 'where her brain had gone and when would it be back?'. She has since had two further pregnancies (including twins) and complained of an additional stepwise deterioration in everyday memory skills following each delivery. Her memory problems are such that she has felt unable to return to work, and has remained a reluctant housewife for the last 16 years. She reported that she frequently forgets appointment times and the appointments themselves. She feels unable to take in any written information the first time she reads it and complains of significant word finding difficulties in conversation. On the WAIS-R she was assessed to function at the top end of the average range with a full scale IQ of 113, consistent with her optimal level of functioning estimated from her educational and occupational history. As with Case I, there was a significant discrepancy between her overall level of intellectual function and her performance on the formal memory tests. Her performance on a test of verbal learning was consistent with her level of intellectual function, however she obtained very poor scores (below the fifth percentile) on a story recall task. She also demonstrated significant difficulties in retrieving information from her general knowledge store.

Although considerably frustrated by their memory lapses, both women denied feeling depressed and were adamant that their memory difficulties dated from the birth of their children and that they were the most significant stressors in their lives.

Discussion

These two cases were seen routinely in the memory clinic and are not presented as definitive case studies. We do not know how prevalent complaints such as these are in the general population of mothers. Similarly, no information is available on possible risk factors.

However, Poser et al (1986) mention two similar cases in their discussion. It is, of course, possible that many of the memory difficulties reported by our patients and those in the literature reflect a partial breakdown in the memory system caused by the stresses of pregnancy and motherhood. However the pattern of deficits on routine clinical testing cases (a specific difficulty in the initial registration of verbal material) and the nature of the subjective complaints of our patients prompted us to investigate whether pregnancy or childbirth may compromise hippocampal function, since the neuropsychological profiles and complaints of these women were remarkably similar to those of patients with known hippocampal damage.

Lesions to the left mesial temporal lobe structures and in particular the hippocampus have long been associated with deficits in performance on verbal memory tests (Baxendale, 1995; Jones-Gotman, 1987), particularly story recall tasks (Delaney et al. 1980; Lencz et al, 1992 ;Moore & Baker, 1996). Recently a number of studies have found a significant correlation between MRI measures of left hippocampal integrity and performance on story recall tasks (Baxendale et al, 1998; Lencz et al. 1992 . Whilst the behavioural correlates of right hippocampal damage have generally proved more difficult to quantify (Rausch & Babb 1993; Sass et al. 1992) poor performances on verbal memory tasks have also been

reported in patients with right hippocampal damage (Delaney et al 1980; Oxbury & Oxbury 1989; Ribbler & Rausch 1990; Saling et al. 1993). In addition, a number of studies have found specific deficits in the learning and recall of non verbal, visual material in patients with right hippocampal damage (Delaney et al. 1980; Helmstaedter et al. 1991; Jones-Gotman 1996)

Thus it is possible that some of the longstanding memory deficits following pregnancy may have an anatomical substrate in hippocampal damage. In the next section we review the hormonal changes that occur during pregnancy and childbirth and examine the evidence for any cognitive changes that they may cause.

Pregnancy, hormones and memory

Pregnancy results in marked alterations in both psychology and physiology (Davey 1995). In particular, many hormones have altered levels in pregnancy (Speroff et al. 1994), and four groups of these hormones are known to influence brain structures involved in memory. These are estrogens, progesterone, glucocorticoids, and oxytocin. In the following section we review the changes in these hormones during pregnancy and their potential effects on memory function.

Estrogens

There is a very large increase in circulating levels of estrogens during pregnancy. It has been calculated that estrogen production in the last weeks of pregnancy is increased 1000 times compared to the rate before conception (Casey et al. 1993). The three predominant

estrogens are estrone (E1), estradiol (E2) and estriol (E3); all three have raised plasma levels during pregnancy (figure 1).

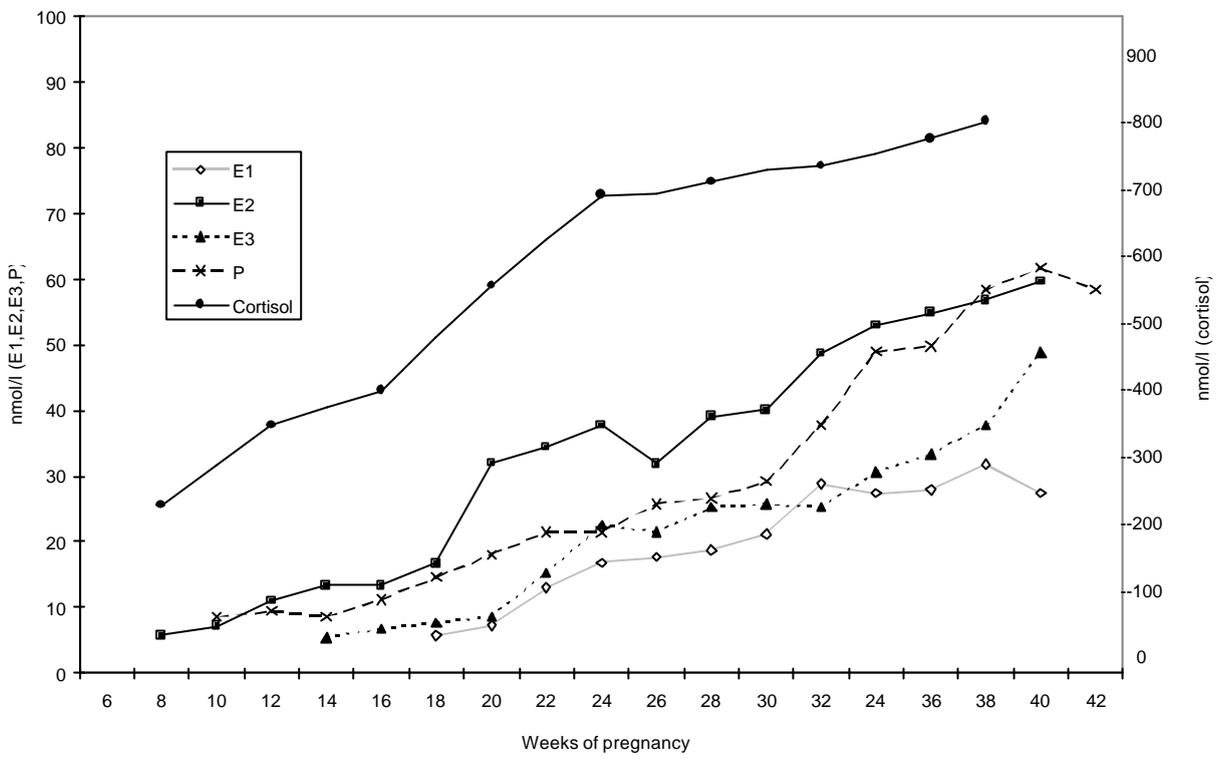


Figure 1

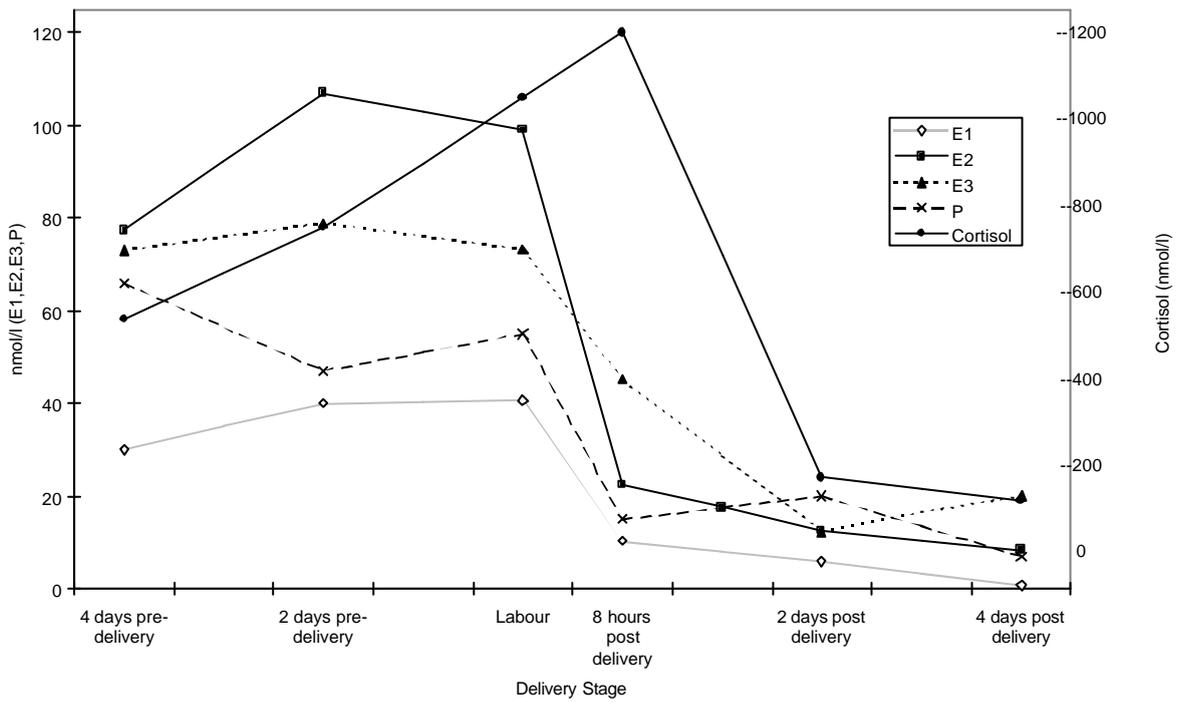


Figure 2

The increased production of estrogens depends on the placenta, therefore levels fall rapidly within minutes of delivery (figure 2) (Munson et al., 1970; Reyes et al., 1972 ;West & McNeilly 1979; Willcox et al., 1985). E3 levels appear to fall off more slowly than those of E1 and E2, probably because the lower plasma protein binding of E3 allows higher fat and interstitial fluid concentrations which equilibrate slowly with plasma (Klopper et al. 1978).

The actions of estrogens on memory structures in the brain have been the subject of recent reviews (McEwen et al. 1995;1997) . The main density of brain estrogen receptors (ERs) are in the hypothalamus, where they are thought to be involved in hormone regulation and the control of reproductive behavior. There are also lower densities of ERs in brain structures involved in memory; notably in the basal forebrain (Pfaff, 1980) and hippocampus (Loy et al. 1988; Maggi et al. 1989). The basal forebrain contains cholinergic neurones that project to the hippocampus and cerebral cortex. Loss of function in these neurones may be the cause of memory impairment in normal volunteers taking anticholinergic drugs (Drachman 1977), and their decline has been related to the memory impairment of aging and Alzheimer's disease (Barthus et al. 1982). Estrogens appear to have specific effects in maintaining cholinergic function in the basal forebrain. Female rats that have been deprived of estrogen by ovariectomy (OVX) show decreases in cholinergic function in these neurones which are at least partly reversed after estrogen replacement (Luine & McEwen 1983 ;Singh et al. 1994).

In the hippocampus, estrogen has striking effects on dendritic spine density. The hippocampi of female rats after OVX show a marked decrease in hippocampal neurone spine density (Woolley & McEwen 1993), which is related to the number of neuronal synapses (Woolley & McEwen 1994). Spine density is restored after a few days of estrogen replacement (Woolley & McEwen 1993). This phenomenon is likely to be physiological because there is a similar decline in spine density in phases of the rat estrous cycle with low estrogen levels (Woolley & McEwen 1994). To our knowledge, there have been no studies on the effect of the combined long term elevation of estrogen and progesterone that occurs in human pregnancy.

The net effect of increasing estrogen levels seems to be an increase of hippocampal excitability. The estrogen peak in the pro-estrus phase of the rat estrous cycle is associated with increased hippocampal long term potentiation (Warren et al. 1995), decreased seizure threshold (Newmark & Penry 1980; Teresawa & Timiras 1968), and increased spontaneous neuronal firing (Kawakami et al. 1970). E2 treatment in rats facilitates acquisition of kindled seizures in the dorsal hippocampus (Buterbaugh and Hudson, 1991), and increases synaptic excitability (Wong and Moss, 1992). Some women who suffer from epilepsy have an increased incidence of seizures during the estrogen peak of the menstrual cycle (Newmark & Penry 1980). This increase in excitability is likely to be due in part to the increase in dendritic spine density in the hippocampus, as the synapses on these spines are excitatory. However, some estrogen effects on nerve cells appear to be too rapid to occur via action on the ER, and suggest direct action on a membrane receptor (Baulieu &

Robel 1995; Gu & Moss 1996; Mermelstein et al. 1996; Wehling 1997; Wong & Moss, 1992).

The increase in neuronal excitability caused by estrogens may predispose to excitotoxicity. Estrogen metabolism can also be harmful to cells in some circumstances. Metabolism of E2 in high doses may result in reduction-oxidation (redox) cycling of E2 metabolites, which results in the formation of free radicals (Liehr & Roy 1990). However, we know of no research looking at these reactions in neurones.

These structural and chemical changes induced by estrogens may be the basis for estrogen-induced changes in memory performance in both rats and humans. A number of lines of evidence suggest that lack of estrogens cause reductions in memory performance, which are reversible after estrogen replacement. In rats, Singh et al (1994) have shown that OVX causes a decline in avoidance learning which is at least partially reversed by estrogen replacement. O'Neal et al (1996) found that OVX rats that had had estrogen replacement performed better on a spatial memory task than OVX controls.

In women, estrogens seem to have a particular role in verbal memory. Sherwin and her colleagues (1988;1994;1990) have studied memory performance in women having bilateral ovariectomy for benign disease. She found that women given placebo post-operatively scored significantly worse on recall of a paragraph of a story than women treated with estrogen, and that this deficit was reversible with subsequent estrogen replacement (Phillips & Sherwin 1992) . Paragraph recall is a task which is particularly sensitive to hippocampal

damage (Baxendale et al. 1998; Delaney et al. 1980; Lencz et al. 1992 ; Moore & Baker 1996). Although there are conflicting reports (see Sherwin 1994 for discussion and review), the same pattern seems to hold for women after the menopause. Kampen and Sherwin (1994) found that postmenopausal women taking estrogen replacement therapy had higher scores on paragraph recall than untreated women.

Thus estrogens seem to play a role in maintaining or even augmenting memory, possibly by their actions on basal forebrain cholinergic neurones and hippocampal synapse formation. Certainly reduced levels of estrogen appear to have a detrimental effect on memory skills. These effects can be reversed if normal levels are restored. However the effect of very high levels of estrogen on memory skills is unclear, and in particular, there is little evidence to suggest that very high estrogen levels have a beneficial effect on memory. The net effect of estrogens seem to be excitatory, perhaps predisposing to excitotoxic damage, and it is possible that estrogen metabolism is toxic to cells in some circumstances.

Progesterone

Like estrogens, progesterone levels rise dramatically during pregnancy, reaching peak levels of around 600 nmol/L, compared to early pregnancy levels of 80 nmol/L (figure 1) (Tulchinsky et al. 1972; Willcox et al. 1985). Like estrogen, progesterone readily crosses the blood brain barrier; indeed, the brain is a significant site of progesterone metabolism (Little et al. 1975). Progesterone has its classical action via the intracellular progesterone receptor (PR), a protein of the steroid receptor superfamily (Speroff et al. 1994).

Progesterone is synthesised by the placenta, and falls off very rapidly after placental separation (figure 2) (Llauro et al. 1968 ;Reyes et al. 1972; West & McNeilly 1979 ;Willcox et al. 1985).

Deoxycorticosterone (DOC) is an important metabolite of progesterone that increases tenfold during pregnancy (Brown et al. 1972; Dorr et al. 1989; Nolten et al. 1978;1979 Parker et al. 1980; Wintour et al. 1978). Because the majority of DOC derives from progesterone in late pregnancy, we would expect DOC to fall rapidly after delivery, although we know of no studies that show this. However, two weeks after delivery DOC levels are near prepregnancy levels (Wintour et al. 1978). DOC has little activity at the PR (Spilman et al. 1986), and weak glucocorticoid activity (Vinson et al.1992), which is unlikely to be important compared to that of cortisol, which has much higher plasma levels (see below).

The actions of progesterone on brain memory structures have been less studied than those of estrogens. Progesterone seems to influence estrogen effects on the hippocampal dendritic spine density; McEwan et al (1993) have shown that dendritic spine density in the hippocampus declines slowly as estrogen levels fall, but that this decline is much more rapid if progesterone is administered during the fall in estrogen levels. The same rapid decline occurs during the estrous cycle of the rat, when estrogen is falling and progesterone levels are high. The rapid down-regulation of dendritic spines is probably due to progesterone's action at the PR, because a progesterone antagonist at the PR, RU 38486, blocks the effect (Woolley & McEwen 1993).

However, progesterone may have important actions other than those mediated by the PR. It has long been known that progesterone in high doses can cause somnolence in animals and man (Merryman et al. 1954). (Merryman et al., 1954; Seyle, 1941). This finding led to the discovery that major metabolites of progesterone and DOC have very high affinity for GABA receptors in the brain (see (Paul and Purdy, 1992) for a review). Specifically, 3 α -hydroxy-5 α -pregnan-20-one (allopregnanolone) and 3 α , 21-dihydroxy-5 α -pregnan-20-one (allotetrahydroDOC), which are progesterone and DOC metabolites, respectively, act on GABA receptors with 1000 times the potency of barbiturate anaesthetics. These 'neuroactive steroids' have a benzodiazepine-like action, increasing GABA activated chloride ion currents and therefore inhibiting neuronal firing. Their very high potency at the GABA receptor has suggested that these substances play a physiological role in regulating neuronal excitability. This view has been strengthened by the observation that allopregnanolone levels increase markedly in rat brain during acute stress, high progesterone phases of the estrous cycle, and during pregnancy (Corpechot et al., 1993; Paul and Purdy, 1992). In man (Freeman et al., 1993) and in rats (Freeman et al., 1993), plasma allopregnanolone levels were highly correlated with progesterone levels, and there is a marked increase in plasma allopregnanolone level during human pregnancy, to an average in the third trimester of near 100nmol/L (Paul and Purdy, 1992), which is likely to result in significant activity at the GABA receptor. Progesterone and allopregnanolone can both be synthesised by glial cells (Schumacher and Baulieu, 1995), and brain levels of the neuroactive steroids may be higher than plasma levels (Corpechot et al., 1993). The neuroactive steroids may have long term effects on GABA receptors; chronic neuroactive

steroid treatment results in downregulation of mRNA for GABA receptor subunits (Yu et al., 1996a), and reduced responses to GABA in isolated cortical neurones (Yu et al., 1996b). If this downregulation occurs during pregnancy, as we might expect, then the rapid fall of progesterone metabolites post partum may expose downregulated receptors. The downregulated receptors could decrease the capacity for inhibition and therefore increase excitability. This may be the explanation for the increase in seizures that women with epilepsy experience during labor and delivery (Tomson, 1997). Seizures are also more frequent in women just before the menses, when progesterone levels drop sharply (Newmark and Penry, 1980).

Progesterone itself may act directly on neuronal membrane receptors to modulate other neurotransmitters; progesterone is reported to influence noradrenergic function in the hippocampus (Monnet et al. 1995), glycine transmission (Wu et al. 1990), and oxytocin receptor expression in the hypothalamus, probably via membrane receptors (Schumacher et al. 1990).

The overall effect of increasing levels of progesterone and its metabolites appears to be neuronal inhibition; progesterone increases seizure threshold in animal models of epilepsy (Frye 1995 ;Newmark & Penry 1980) and the high progesterone levels of the luteal phase of the menstrual cycle are associated with lower seizure incidence in some women with epilepsy (Mattson & Cramer 1985; Newmark & Penry 1980).

In view of the effects of progesterone and its metabolites on the brain, it is perhaps surprising there have been so few studies of the effects of these steroids on memory. However, in rats allopregnanolone implanted in the cerebral ventricles resulted in poorer performance in the Morris water maze, a test of spatial memory (Frye & Sturgis 1995). Freeman and her colleagues tested memory performance after large doses of oral progesterone to healthy women volunteers (Freeman et al. 1992;1993). The higher doses gave progesterone blood levels comparable to those in late pregnancy, and these levels resulted in significant impairment at paragraph recall. The concentration of allopregnanolone after the oral progesterone dose was a better predictor of poor memory performance than progesterone level, suggesting that the memory deficit might be related to allopregnanolone rather than progesterone itself.

Thus the primary action of progesterone on memory may be due to its metabolites which have a highly specific action in increasing neuronal inhibition via the GABA receptor. The downregulation of GABA receptors caused by progesterone metabolites may cause a reduction of inhibition when progesterone metabolite levels fall rapidly, as they do after delivery.

Glucocorticoids

Glucocorticoids act on two intracellular corticosteroid receptors, type I (mineralocorticoid receptor - MR), and type II. (glucocorticoid receptor - GR). In man, the most potent glucocorticoid is cortisol; although both corticosterone and DOC have some glucocorticoid activity (Vinson et al., 1992), plasma levels are much lower than those of cortisol, and they

are likely to exert a much smaller glucocorticoid effect. Cortisol increases during pregnancy, although to a lesser extent (relative to levels before pregnancy) than estrogen or progesterone. (figure 1). There is a marked increase in cortisol levels during labour (Bayliss et al. 1955; Dorr et al. 1989; {Jolivet, Blanchier, et al. 1974 ID: 697}; Sippell et al., 1978; Willcox et al., 1985), which has been attributed to maternal stress. After placental separation, cortisol levels fall less dramatically than the sex hormones (figure 2). Unlike estrogens and progesterone, cortisol levels continue to be raised for several weeks after delivery (Wintour et al. 1978).

The control of cortisol secretion and interpretation of plasma levels becomes considerably more complicated during pregnancy. Progesterone has significant binding activity *in vitro* for both the mineralcorticoid and glucocorticoid receptors. In man progesterone is likely to act as an effective antagonist at both receptors, but to a considerably greater extent at the MR (Rupprecht et al. 1993). This may be important during late pregnancy, when progesterone and cortisol levels are comparable. At these concentrations, progesterone competes with cortisol for glucocorticoid binding (Nolten et al. 1980). The raised levels of cortisol in pregnancy could be a physiological adaptation to GR and MR antagonism by progesterone. This may explain the lack of overt Cushingoid symptoms during pregnancy despite raised cortisol levels, and the fact that feedback control of ACTH release seems to be reset at a higher level of plasma cortisol (Peterson & Klopper 1983).

There is a considerable literature on the effects of glucocorticoid on the brain, and in particular on the hippocampus. Some areas of the brain, including periventricular and hypothalamic regions thought to be involved in salt balance, contain MR which has functional

selectivity for mineralocorticoids, presumably because of local enzymatic breakdown of glucocorticoids, as occurs in the kidney (de Kloet et al. 1994). Outside these areas, MRs are not selective for aldosterone, and therefore will be predominantly influenced by glucocorticoid levels. The animal literature suggests inconsistencies between species regarding the distribution of corticosteroid receptors. Non-selective MRs are distributed throughout the rodent and rhesus brain, but both have a high density in the hippocampus (Sanchez et al. 2000). However the monkey brain does not reflect rodent GR distributions. Whilst rodent and human post mortum studies suggest high GR density in the hippocampus (de Kloet et al. 1994; Sarrieau et al. 1986) recent primate work has demonstrated that the rhesus hippocampus does not contain a significant amount of GR receptors, these being found mostly in the neocortex, particularly in the frontal regions (Sanchez et al. 2000). The roles of the two receptor types are not fully understood, but it seems that MR activation increases hippocampal sensitivity to excitation, whereas GR activity tends to suppress neuronal excitability (de Kloet et al. 1994; Joels & de Kloet 1992; Pavlides et al. 1995).

It is probably MR and GR that mediate the dramatic hippocampal cell loss that occurs after reduction or increase of circulating glucocorticoid levels (Sapolsky 1994). In addition, it has been shown that the hippocampal neurones of animals with moderately raised glucocorticoid levels are more sensitive to damage caused by a wide variety of insults, such as hypoxia, prolonged generalised seizures, hypoglycaemia, oxygen free radical generators and excitotoxins (Sapolsky 1994). This so-called 'glucocorticoid endangerment' of the hippocampus may be mediated mainly by the GR (Packan & Sapolsky 1990), and in particular by GR mediated reduction of cell glucose uptake, thus making hippocampal cells

more sensitive to situations that require an increase in cell metabolism (Horner et al. 1990). For example, supplementing the energy supplies of neurones with glucose protects them from glucocorticoid endangerment from hypoxia, hypoglycaemia, excitotoxins and free radicals (Sapolsky 1985; Sapolsky et al 1988; Tombaugh et al. 1992).

The high circulating glucocorticoid and progesterone levels during pregnancy are likely to alter expression of GR and MR, but the extent of the alteration is not easy to predict. Regulation of receptor levels is complex (de Kloet et al., 1990), and there are species differences even between rat (Reul et al., 1989) and mouse (Luttge and Rupp, 1989). However, it appears that both MR and GR activation cause downregulation of GR, whereas GR activity causes upregulation of MR (O'Donnell and Meaney, 1994; Reul et al., 1989; Reul et al., 1987). Progesterone exerts a strong antagonism on the MR, and weak antagonism at the GR (Rupprecht et al., 1993). As glucocorticoid levels are only moderately increased during pregnancy, progesterone may cause functional blockade of the MR, whereas GR activity should be increased or unaltered. This situation may cause an increase in MR levels, and a decrease in GR levels. Progesterone also appears to act directly via the PR to increase MR levels (Castren et al., 1995), possibly further increasing MR levels during pregnancy.

The demonstrated effects of glucocorticoid on hippocampal neurones may be the cause of observed memory deficits in animals and man after excess glucocorticoid. Thus, both stress and chronic glucocorticoid excess may cause spatial memory deficits in rats (Bodnoff et al. 1995; Conrad et al. 1996; Luine et al. 1994). In man, synthetic glucocorticoids cause a

specific reduction in verbal recall scores in normal volunteers (Newcomer et al. 1994), and in patients taking therapeutic doses of steroids (Keenan 1996 ;Keenan et al. 1995).

Patients with Cushing's Syndrome (CS), who have an endogenous overproduction of cortisol, also have deficits in verbal recall (Mauri et al. 1993; Starkman et al 1992). The latter study also used high quality MRI scans to measure hippocampal volume in patients with CS, and found hippocampal volume was reduced compared to the normal range, and that this reduction was correlated with memory impairment and plasma cortisol levels . In both volunteers, and patients with CS, memory performance improved with reduction in the excess glucocorticoid (Newcomer et al. 1994; Mauri et al. 1993).

Thus, excess glucocorticoids have an adverse effect on memory, and may cause long-lasting damage to the hippocampus. In addition, they predispose the hippocampus to coincident damage by excitotoxicity, and other insults. Activation of the MR tends to increase hippocampal excitability, and activation of GR reduces excitability.

Oxytocin

Oxytocin is a peptide hormone that is synthesised by cells in the hypothalamus and released from the posterior pituitary. The changes in oxytocin levels during pregnancy have been reviewed by Dawood (1983). There is a peak of oxytocin secretion during the second stage of labour, to average levels of around 100 pmol/L, followed by a rapid decline following delivery. Suckling causes a spurt of oxytocin release, giving brief but variable increases of plasma levels to around 40 pmol/L in breast feeding mothers.

Oxytocin is known to act on only one type of membrane receptor. There are oxytocin receptors in various brain regions, including the hippocampus, striatum and amygdala (de Wied et al. 1993). Increases in oxytocin levels in rat brain are associated with reductions in active and passive avoidance learning, although its effects depend on the exact nature of the task (Engelmann et al. 1996). There is some evidence that high doses of oxytocin cause deficits in verbal recall in man (Ferrier et al., 1980; Kennett et al., 1982), although the finding has not been consistent (Fehm-Wolfsdorf et al., 1988). Interestingly, Geenen et al (1988) found that oxytocin caused a significant and long-lasting reduction in contingent negative variation, an EEG correlate of motor learning, although there was little effect on memory performance in their study. The relevance of these findings to pregnancy is not clear; Silber et al (1990) measured performance on various memory tasks and serum oxytocin levels in 20 women before and after delivery and found no overall correlation between scores of memory tests and oxytocin levels.

The causes of memory loss associated with pregnancy

Our review of the memory in pregnancy literature and case reports have suggested the possibility of two syndromes of memory loss associated with pregnancy. The first we would characterise as gestational memory impairment (GMI). GMI seems to occur in up to 80% of pregnancies, often in beginning in the second trimester, and continuing through the third. GMI appears to be characterised by a high level of subjective memory complaints and an objective impairment on explicit memory tasks. In most women, the memory impairment

appears to resolve soon after childbirth, although there is little direct evidence to support this. The second syndrome is that of prolonged post-partum memory impairment (PPMI). This memory loss seems to date from childbirth, rather than pregnancy, and to be long lasting. This appears to be much rarer than gestational memory impairment, although the lack of longitudinal studies of memory following childbirth means that the true prevalence of such complaints is unknown.

If such syndromes of memory loss do occur, what are their likely causes? The most obvious causes are psychological stresses associated with pregnancy and childcare. However whilst this area is not well researched there are a number of pointers in the literature that suggest that some of these memory complaints may have an organic basis. In our review, we have concentrated on the hormonal changes of pregnancy, because several hormones that are elevated during pregnancy have specific effects on memory. We have also suggested that the patterns of memory loss both during and after pregnancy have features of hippocampal dysfunction. In our cases, the pattern of memory loss was consistent with reduced hippocampal function, with impaired recall, but not recognition, and no impairment in non-memory tasks. We therefore propose that both GMI and PPMI may be partly the result of hormonal action on the hippocampus.

The causes of GMI

Of the hormones that we have discussed, we suggest that progesterone and glucocorticoid are the two most likely to influence memory during pregnancy. In isolation, we would expect the prolonged rise in plasma cortisol to reduce memory performance, in the same

way as it does in Cushing's Syndrome (CS). Glucocorticoids may affect memory by causing cell loss in the hippocampus, or by its effects on neuronal excitability. In any case, the memory loss of CS and following treatment with synthetic glucocorticoids seems to be reversible, at least to some extent. However, the elevation of glucocorticoids during pregnancy differs from that of CS. Firstly, glucocorticoid levels during pregnancy are lower than those seen in CS (Burke & Roulet 1970). Secondly, progesterone, which reaches very high levels during pregnancy, is an antagonist for glucocorticoid, especially at the MR, and this may well be the reason that women do not have clinical CS during pregnancy. Thirdly, if glucocorticoids exert their main effect by damage to the hippocampus, then we might expect that most women would suffer from some degree of permanent memory loss post-partum, which does not seem to be the case.

Progesterone is another candidate for the cause of GMI. As we have discussed above, some metabolites of progesterone have benzodiazepine-like actions, increasing neuronal inhibition by acting on the GABA receptor. These metabolites are highly correlated with progesterone levels, and are greatly increased during pregnancy (Paul & Purdy 1992). The metabolite levels are likely to fall very quickly after delivery, as do those of progesterone, and this would explain the observation that normal memory function probably returns rapidly after pregnancy for most women. Oral doses of progesterone that give late pregnancy blood levels of progesterone and its metabolites cause significant memory dysfunction on tasks that require hippocampal integrity (Freeman et al. 1992; 1993). There is also some indirect evidence for the role of progesterone metabolites in memory dysfunction in the study by Brindle et al (1991). They noted an unexpected *positive* correlation between memory

performance and anxiety levels. If, as we propose, high levels of progesterone metabolites are responsible for both memory impairment and reduction in anxiety, then this might explain their finding. We therefore suggest that it is in fact the progesterone metabolites which are the primary cause of GMI.

The causes of PPMI

The pattern of memory loss in our cases of PPMI appears to be similar to that seen in other patient populations with hippocampal lesions. It is possible that the memory deficits reflect the same processes as those that cause GMI; for example, the raised glucocorticoid level during pregnancy may cause hippocampal cell loss, or perhaps the raised estrogens allow redox cycling and free radical formation causing hippocampal damage. However, it is also possible that PPMI is due to a neurochemical lesion to the hippocampus caused during or soon after childbirth. There are several major hormonal changes influencing the hippocampus during pregnancy. The estrogen increase will tend to increase hippocampal excitability, and dendrite formation. These effects will be opposed by the increases in progesterone, which may decrease hippocampal excitability, most notably by the direct inhibitory effects of its metabolites at the GABA receptor. At the same time, glucocorticoid levels increase. Because progesterone is a stronger antagonist for the MR than the GR, we might expect there to be a functional excess of GR activity, and perhaps a drop in MR activity. This may lead to an additional inhibition of the hippocampus, due to the opposing effects of the MR and GR on hippocampal excitability. In addition, the MR receptor may be up-regulated, and the glucocorticoid receptor down-regulated. Very soon after delivery, E2 and progesterone levels drop very sharply. Estriol (E3) levels also drop rapidly, but then

reach a plateau, and remain moderately raised for some days (Klopper et al. 1978). Glucocorticoid levels reach a peak during labour, and remain raised, relative to non-pregnant levels, for several weeks (Wintour et al. 1978). A few hours post-partum the hippocampus is in a state of flux. It has had a dramatic drop in inhibition as the progesterone metabolites drop, probably exposing down-regulated GABA receptors. This situation may result in increased neuronal excitability. E3 is now acting unopposed by progesterone, and the same is true of cortisol, which may be acting on up-regulated MR, further increasing neuronal excitation. It seems plausible that the combined effect of these changes would make the hippocampus particularly vulnerable to insult, such as hypotension, hypoxia, or hypoglycaemia, or that the increase in excitability may lead to excitotoxic damage to the hippocampus. Clearly, however hippocampal damage does not occur in the majority of labours. The individual factors associated with increased risk during the proposed period of hippocampal endangerment will depend on the unique levels of hormonal flux and any predisposing factors which will be different not only for every women, but for every pregnancy and delivery she experiences. Thus we do not propose that every pregnancy has an exponential detrimental impact on the hippocampus. Increased memory deficits as a function of the number of children born are more likely to have an environmental (rather than structural) origin in the divided attention capacity of the mother. The factors that may protect women from, or predispose women to, hippocampal damage during labour are unknown but there is considerable inter-individual variability in the hormonal fluxes experiences during labour as evidenced by the very different lengths of and experiences associated with childbirth. We have presented a hypothetical model, based on known hormonal characteristics that may expose the hippocampus to damage in some cases. More

research is needed to establish the specific risk factors for this condition to arise and to explain the clearly evident inter-individual variability.

Testing the hypotheses

In this review we have suggested that two syndromes of memory disturbance may be associated with pregnancy and childbirth. However, memory loss following pregnancy and childbirth has not been well researched, and whilst anecdotal evidence abounds, rigorous research designs have yet to be applied. Clearly, if these ideas are to be taken further the first step will be to establish the existence, prevalence and clinical significance of GMI and PPMI. If they do exist as discrete syndromes, the next step will be to establish the extent of both the organic and psychological bases of the complaints. The second part of this paper has reviewed some aspects of the neuroendocrinology of pregnancy and suggested some hypotheses to explain the physiological basis of memory disturbance associated with pregnancy. We have focused primarily on the hippocampus, although this is by no means the only brain structure involved in memory that may be affected by the endocrinological changes that occur during pregnancy and labour. To test these hypotheses we need a prospective study with careful memory testing and hormone level measures during pregnancy and for at least a year post partum. Our model predicts that memory disturbance during pregnancy will correlate with progesterone and progesterone metabolite levels, rather than glucocorticoid levels. Memory loss during pregnancy may dissociate from memory loss after pregnancy, and memory loss after pregnancy may not correlate with pregnancy glucocorticoid levels. High maternal cortisol after pregnancy and during labour may

predispose to PPMI, as may post-partum estrone levels and a precipitous drop in progesterone levels following delivery. Hypoglycaemia during labour and post partum may also predispose women to PPMI due to the associated glucocorticoid energy influx block.

In addition to these theoretical interests, the further study of GMI and PPMI may have important clinical implications. A large proportion of mothers may be at risk of GMI and antenatal care may be improved if women are formally prepared for GMI prior to conception or in the early stages of pregnancy when they can be helped to develop memory strategies to overcome the impending difficulties. It may also be possible to identify risk factors that predispose some women to developing the more serious PPMI and plan interventions accordingly. We very much hope this review will provoke further discussion and stimulate a multidisciplinary approach to future

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Acknowledgements

We would like to thank Dr Stavia Blunt for her very helpful comments in the preparation of this review.