Original Research Article

Role of sex hormones in female migraineurs

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Abstract

Migraine is a chronic neurological condition with episodic exacerbations. Pain is accompanied by autonomic symptoms, the most common being nausea, vomiting, photophobia and phonophobia. Migraine triggers include dietary factors, hormonal changes, environmental factors, physical activities and psychological and chronobiological changes. Female migraineurs are normally influenced by hormonal changes as migraine varies with female reproductive events like menopause, menstruation, oral contraceptive use, hormonal replacement therapy etc. Hereby, presenting a paper on survey conducted to assess exacerbation of migraine attacks in proportion with fluctuating levels of female sex hormones before, during and after pregnancy.

Key Words: Migraine, Menstruation, Menopause, Pregnancy, Women, Sex Hormones.

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INTRODUCTION

The name migraine originally comes from Greek word *hemicrania* meaning 'half of the head', representing one of the most striking features of condition. Equally commonly pain is felt bilaterally, at the front or back of head, rarer in body (migranous carpalia). Pain is accompanied by autonomic symptoms, the most common being nausea, vomiting, photophobia and phonophobia (Headache classification subcommittee of International Headache Society 2004). Globally, migraine afflicts 11% of the total adult population creating a significant socio-economic burden on society. Studies suggest that approximately 1% of world's population have chronic migraine[17]. Migraine occurs in both sexes, but is predominantly found in females with a cumulative lifetime prevalence of 2.46:1 i.e. females are three times more prone to males for migraine[18].

Pathogenesis of migraine

1. It is a primary headache disorder, result of an imbalance in activity in brainstem areas that control pain transmission and regulate blood flow in brain. The hyper excitable occipital cortex of the migraineur can be activated by a variety of environmental and indigenous events to cause a depolarizing neuroelectric and metabolic brain event known as "spreading cortical depression" (SCD) that produces aura in some patients and sets in motion the events that led to headache. SCD triggers the release of neurotransmitters that activate peripheral neurovascular and brainstem pathways and cause blood vessel dilation, inflammation and further nerve activation.
2. A study conducted states "that serotonin and CGRP levels in neuronal tissues are affected by physiological hormonal intervention specifically the estrogen making women predisposed to migraine". Estrogen can act via can genomic or non-genomic mechanism to regulate the levels of neuroactive molecules. Non-genomic mechanism involve the modulation of neurotransmission unrelated to the transcription of genes and may occur within seconds to minutes following estrogen exposure. Estrogen has been found to rapidly increase nitric oxide production in cerebral blood vessels by increasing the phosphorylation of protein kinase B (Akt) and endothelial nitric oxide synthase (eNOS) enzyme through the PI3K/Akt/eNOS pathway. However,

chronic estrogen exposure specifically increases eNOS protein levels through genomic mechanisms involving a receptor-mediated increase in transcription and translation of the eNOS gene. Genomic mechanism of action of estrogen consists of regulation of gene transcription via estrogen receptors (ER) having wide distribution throughout the central nervous system. Estrogen receptors may be membrane-bound or intracellular and are of two types: ERα and ERβ. ERα is expressed in trigeminal neurons while ERβ is within the dorsal raphe. Estrogen binds to its receptors and either causes receptor dimerization or activates secondary messenger system such as cAMP/protein kinase A, protein kinase C, MAP kinase/ERK etc. The estrogen-receptor complex or the secondary messengers enter the nucleus and bind to DNA regulatory regions as AP-1 sites, estrogen response element (ERE), cAMP response element (CRE) and serum response element (SRE) to regulate the transcription of various genes. Data obtained by various studies has shown up-regulation of the serotonergic system during the mid-menstrual cycle (high estrogen) while during the mid-luteal and early follicular phases (low estrogen), there is down-regulation of the serotonergic system. Durham and coworkers have investigated the control of CGRP expression by a serotonergic agonist and demonstrated that the activation of the endogenous 5-HT1 receptor is coupled to calcium signaling pathways leading to inhibition of CGRP gene transcription by repression of promoter activity through CRE and a cell-specific enhancer. Elevated calcium can inhibit CRE binding protein (CREB) activity by stimulating a CREB phosphatase and by causing an inhibitory phosphorylation of CREB. This finding raises a possibility that serotonin system and CGRP are linked to each other in bringing about migraine pathophysiology [14].

Phases of migraine: The signs and symptoms of migraine are variable and include the four phases of prodrome, aura, pain and postdrome that are common among patients but are not necessarily experienced by all migraine sufferers.

1. Prodrome-Several hours or days before the headache, patient experiences irritation, depression, excessive sleep, increased urination, muscle stiffness (especially of the neck), constipation or diarrhea etc. that constitutes the prodrome phase.
2. Aura-Symptoms of migraine aura appear gradually for 5 to 20 minutes which can be visual, sensory (numbness) or motor in nature and generally lasts less than 60 minutes. Visual disturbances are extremely painful with bright flashing lights, black spots or partial loss of vision.
3. Pain-Then migraine pain occurs which may be bilateral at the onset or gradually start on one side and become generalized, usually alternating sides from one attack to the next. The extremities tend to be cold and moist. The frequency of attacks is extremely variable, from a few in a lifetime to several times a week with an average of one to three headaches a month.
4. Postdrome-After an attack in the postdrome phase, some people feel unusually refreshed or euphoric while others undergo depression or experience tiredness, irritability, listlessness, impaired concentration, scalp tenderness or mood changes

Classification of migraine: The International Headache Society has classified the different types of migraine and described it in "International Classification of Headache Disorders, 2nd. Edition (ICHD-2)" *Migraine without aura* – This is the most common form and accounts for 80% of cases reported with migraine headache. *Migraine with aura* – This constitutes second most common form with the diagnostic criteria as aura associated with fully reversible visual or sensory symptoms. However, no muscle weakness or paralysis is seen. Approximately 10% of the migraineurs experience this classical type.

Common triggers

1. Changes in routine: Some people find that changes in their routine can contribute to a migraine. For example changing sleep patterns or changes caused by long journeys can precede an attack.
2. Stress: Migraine and stress are strongly linked. Indeed, anxiety, excitement and any form of tension and shock may all lead to a migraine attack. However, some people report that their migraine attacks start when the stress reduces.
3. Sleep: The complex nature of trigger factors is illustrated by sleep. Both too much and too little sleep can be implicated in a migraine starting. Some people find that sleepless nights, a number of late nights and being over tired can trigger a migraine.

1. Caffeine: Excessive consumption of caffeine may contribute to the onset of a migraine attack.
2. Hormonal changes in women: Migraine is closely associated with female hormones. Some women find their migraines start at puberty, and are linked to their menstrual cycle. The additional hormonal trigger for women may explain why more women than men experience migraine during their reproductive years. The menopause is often the most difficult time for women with migraine.# Menstruation[19] is a migraine trigger in 10% of the females with migraine. One half to three fourth of female with migraine without aura experience a reduction in frequency or total cessation of migraine attack during pregnancy, mainly in second and third trimesters. # 8% of pregnant women having migraine with aura experience increase in attack frequency and pain intensity of migraine throughout pregnancy. # 30-40% of all women experiences postpartum migraine attack mainly during first week of delivery. # A study shows that the risk of 10 or more headaches a month increases by up to 50% as estrogen levels drop and women enter perimenopause, while migraine improves for 67% of women after spontaneous or natural menopause (menopause occurring on an average age of 51 years) but worsens in 67% of women with surgical menopause or induced menopause (cessation of menstruation after either bilateral oophrectomy or iatrogenic ablation of ovarian function).
3. The environment: There are certain trigger factors which can be related to environmental issues such as high altitude, weather changes, high humidity, loud noises, exposure to glare or flickering lights.
4. Food: Food related triggers occur in about 10% of people with migraine[13]. Many people will crave sweet food such as chocolate before the pain of the migraine is experienced which leads them to conclude that eating sweet food is a cause. However, sometimes the craving for particular food is a symptom of the beginning of the migraine. Missing meals or eating sugary snacks instead of a balanced meal can all contribute to a migraine attack. Insufficient food is probably one of the most important dietary triggers.
5. Additives: Some food products contain chemicals or additives which may also be implicated in an attack. Ones which are frequently mentioned by people with migraine are monosodium glutamate, nitrates and aspartame.
6. Alcohol and cheese: There is some evidence that red wine may trigger a migraine because it contains tyramine which has been linked to migraine. Certainly many people with migraine avoid red wine. Tyramine is also found in other food products such as soft cheeses like camembert and brie.
7. Mild dehydration: Mild dehydration can have an impact on people who have migraine. It is recommended that you should drink at least 8 glasses of water per day. This is in addition to any other drinks you may have. Fizzy drinks can contain the sweetener aspartame which some people link to their migraine.

Treatment of migraine: Acute migraine can be managed with conservative measures, such as analgesia, hydration and anti- emetics. Paracetamol and codeine are most commonly used as they are deemed the least harmful during pregnancy. NSAIDS, such as ibuprofen, are contraindicated, especially in the third trimester, as they can cause premature closure of the patent ductus arteriosus. Serotonin receptor antagonists (Triptans), such as Sumatriptan, are used commonly in the non-pregnant population to treat migraines. There is limited evidence regarding the safety of triptans during pregnancy.

Patients suffering with recurrent migraines during pregnancy should be considered for prophylactic treatment. Simple methods include avoiding triggers, ensuring a good sleep and nutrition pattern with moderate exercise and relaxation. Non-pharmacological methods include biofeedback relaxation techniques and acupuncture

METHODOLOGY

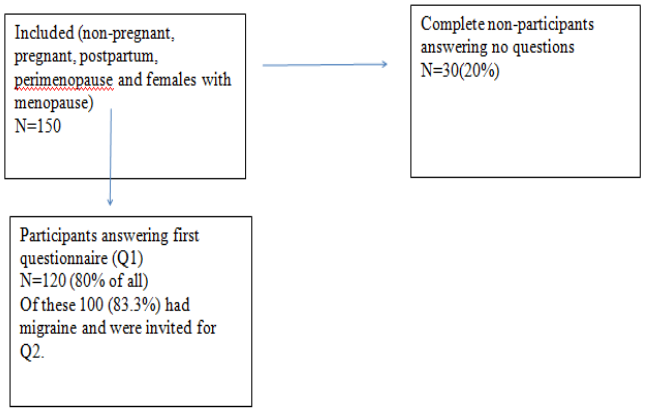
The present cross sectional study was done from July 2017 to January 2018. Simple random sampling of sample size 150 was done. In this female population of age group 15 -50 years was included. Non pregnant, pregnant, postpartum, perimenopause and menopause females having headache were included in study. The purpose of the study was to correlate the role of sex hormones in female migraineurs before during and after pregnancy. All participants were asked to respond to two questionnaires Q1 and Q2. The first questionnaire (Q1) was used for the diagnosis of type of headache. Questions were mainly designed to classify the headache as migraine or not using a modified version of current

migraine criteria of the headache classification committee of international headache society. Participants who fulfilled the criteria for migraine in Q1 were given Q2. Q2 was given to patients 2 weeks after receiving Q1. In Q2 they were asked questions on pain intensity (0-10), nausea, vomiting, photophobia and phonophobia, attack duration (hours), doses and type of acute medication used and level of functioning disability (0-3) (where 0 is normal and 3 is bed ridden).

Data Handling And Statistical Methods: Information based on data collected was summed up to investigate more closely the role of sex hormones, women with migraine were interrogated 2 days before, during and 2 days after menstrual cycle, 1st, 2nd and 3rd trimester of pregnany,1week after delivery, perimenopause period, at the time of menopause (surgical or natural). For independent samples t tests and chi square tests were performed on continuous and categorical variables, respectively. A p value less than 0.05 were considered significant.

RESULTS

The flow of participants through the different steps of survey is shown in fig1. Among all the included participants (150) 120 (mean age 28.5) answered Q1. Among these 120 participants 100 fulfilled criteria to fill Q2 as their headache was classified as migraine. The participants were given Q2 2 weeks after filling Q1 and in mean time they were asked to keep record of frequency of attacks, duration of attacks, triggering factor for attacks etc.



Demographic characteristics of participants are shown in Table 1. The mean age for patient suffering from migraine is 29.5 years (range 15-50, median 29), similar as stated in the MIGRA study.

Table 1:

	Mean age years ± SD
Total participants (n=150)	28.9± 9.9
Patients answering Q1 (n=120)	28.5± 9.8
Patients answering Q2 (n=100)	29.5± 9.9

Prevalence of migraine before pregnancy: 32 participants having migraine before pregnancy were selected for study, which contained three variants i.e. menstrual migraine (50%), genetic migraine (25%), and migraine without unknown etiology (25%).). Menstrual migraine was significantly more common in migraine without aura than in migraine with aura patients ($p < 0.01$).

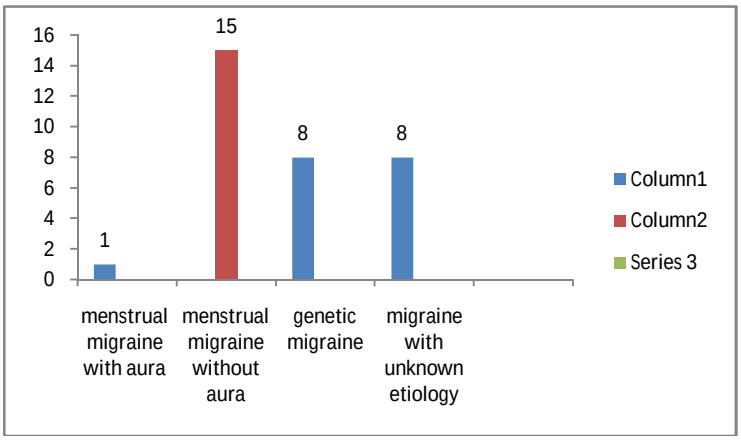


Figure 1:

Change in frequency of migraine during pregnancy and puerperium: Overall 36 out of 100 participants were pregnant females and 12 females with postpartum period were included. The frequency of migraine in first trimester (1 day/week) was higher as compared to 2nd and 3rd (0.5 days/week) in patients having migraine without aura. Those patients having migraine with aura had marked increase in frequency of migraine in all three trimesters (2 days/week). There was a marked increase of episodes after the first week after birth both in patients having migraine with aura and migraine without aura than pregnancy period. The group with freedom from earlier headache during pregnancy did not differ significantly with regard to age ($p>0.2$).

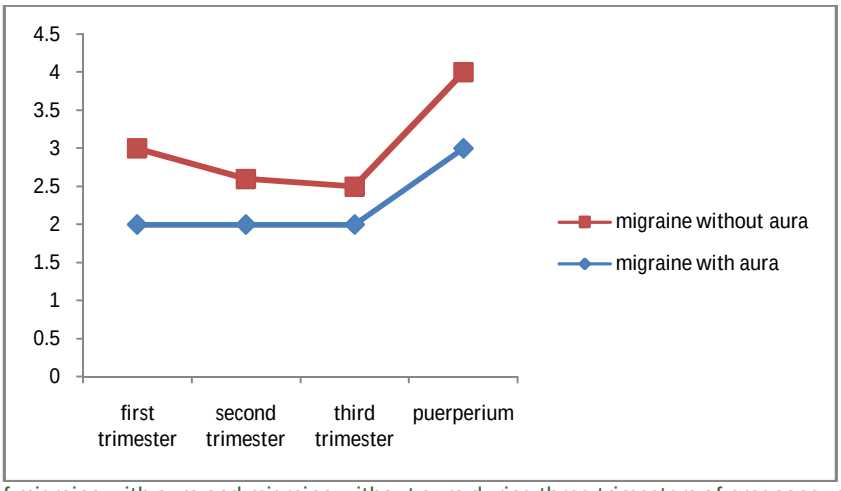


Figure 2: Shows variation of migraine with aura and migraine without aura during three trimesters of pregnancy and puerperium

Change in frequency of migraine in perimenopause and post-menopause: 20 out of 100 female migraineurs were in their perimenopause and postmenopause period. 60% of premenopausal or perimenopausal women reported an increased prevalence of migraine (8days/4weeks) compared to 40% spontaneous or induced menopause women (0-4 days/4weeks).

Also migraine improvement occurred in women after spontaneous menopause (0-1 days /4weeks) as compared to surgical menopause (2days/4 weeks) 16% women having migraine without aura show more improvement after menopause as compared to 2% women having migraine with aura.

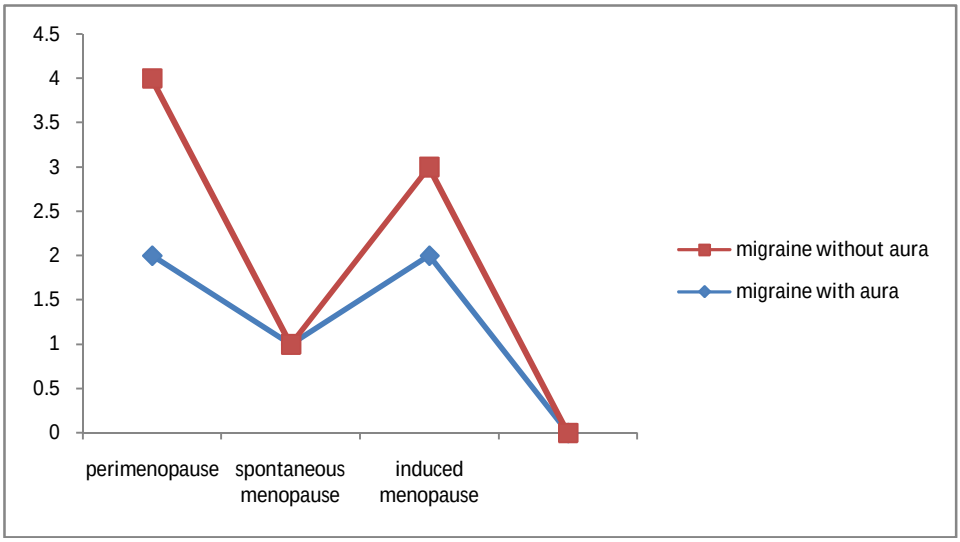


Figure 3:

Change in frequency of migraine during pregnancy and postmenopause: Comparative study of pregnant and postmenopause female migraineurs was done. Frequency of migraine was higher in pregnant women (0.5-2 days/week) than in postmenopausal women (0-1days/week).

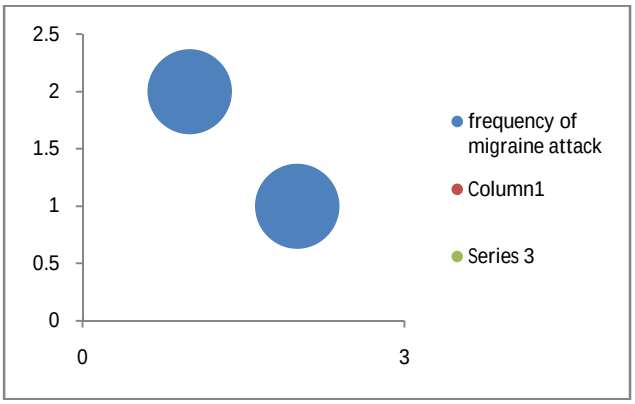


Figure 4:

Characteristics of migraine before pregnancy, during pregnancy, puerperium, perimenopause and postmenopause: There was a significant shortening of duration of headache episodes ($p<0.01$) during pregnancy compared to before pregnancy among female migraineurs. Comparing pregnancy and puerperium, there was a postpartum increase in the mean headache intensity ($p<0.01$), mean headache duration ($p<0.01$), mean number of analgesics used ($p<0.02$) Intensity of headache ($p<0.02$) and duration of headaches ($p<0.01$) increased during perimenopause period when compared to frequency and intensity during pregnancy. Frequency of headache decreased during postmenopause period compared to perimenopause and during pregnancy ($p<0.02$).

DISCUSSION

Methodological considerations: Major strength of the present study are that all women in a certain period of time were invited prospectively, thereby avoiding selection bias. Also detailed questionnaires were used for methodology and that the IHS criteria were used for diagnosing women with migraine. The fact that self-considered migraine constituted only a small proportion of all headaches among the migraineurs point to low awareness of definition of migraine among the participants, indicating that the result should be interpreted with caution. The finding that many women with earlier headache became headache free during pregnancy is consistent with other studies [1-12]. It is interesting to note that this favorable course was more than twice as common as developing new onset headache.

Prevalence of migraine before pregnancy: Prevalence of migraine before pregnancy especially in case of menstrual migraine is associated with migraine without aura than migraine with aura, which is in concord with study[3]

Change in frequency of migraine among migraineurs during pregnancy and puerperium: Our data are in concord with previous studies[10,11,15] Showing a gradual decrease during pregnancy of headaches in general and self-considered migraine towards birth. Scharff *et al.*[11] reported an increase in headache activity around birth and the following 3 weeks, thereby supporting our finding. The peak following delivery may be a result of several factors such as the physical strain of giving birth and the ensuing sleep deprivation and adaptation to the new postpartum situation, as well as psychological factors like anxiety and worry. In addition, during labor several hormones are interacting and possibly affecting neurotransmitter system in the brain which may produce headache.one should also consider the possibility that headaches in the early postpartum period may occur as a side effect of procedures or medication during labor, for example spinal puncture headaches after epidural or spinal anesthesia or use of NO_2 gas. The number of doses of acute medication was lower in pregnancy. The finding is consistent with that of Maggioni *et al.*[5] who reported that use of medication during pregnancy was reduced and restricted to a limited number of compounds.

Change in frequency of migraine during perimenopause and postmenopause: "Headache attributed to exogenous hormones" and "estrogen withdrawal headache" have already been internationally coded as headache diagnoses.1 The fact that both estrogen addition and estrogen withdrawal may trigger a headache with migrainous features suggests that migraine is sensitive to hormonal fluctuations rather than to the amount of circulating hormones. There is some suggestion that hormonally sensitive women (e.g., those who have experienced migraine changes in conjunction with previous hormonal events such as menstruation, pregnancy, and use of oral contraceptives) are more likely to have migraine worsening in the perimenopause. Women with a history of menstrual migraine may be more vulnerable to exacerbation of migraine during the hormonally unstable perimenopausal period.[16] The transition from reproductive to non-reproductive phase is the result of a progressive reduction in female hormonal production by the ovaries and usually lasts 4–8 years. Although the perimenopausal period is characterized by considerable fluctuations of estrogen and progesterone levels, greater than those occurring during the normal phases of menstrual cycle in the fertile period, menopause is characterized by hormonal stability due to the decline of estrogen and progesterone production by the ovaries.3 During perimenopause, the slower these hormonal changes occur, the greater the improvement of migraine. The achievement of hormonal stability on menopause is positively associated with migraine improvement.

Change in frequency of migraine during pregnancy and menopause: A comparative study between the two different phases of female reproductive cycle, pregnancy and menopause showed that migraine is precipitated more during pregnancy due to hormonal fluctuations while due to stability of hormonal levels during menopause frequency of migraine decreases which is in concord with study[4].

CONCLUSION

Current literature has consistently demonstrated that migraine is more prevalent in women as compared with men, specifically during reproductive years. Recent studies have found differences in headache characteristics, CNS anatomy as well as functional activation by fMRI between the sexes in migraine patients. Although the cause underlying these differences is likely multi-factorial, considerable evidence supports an important role for sex hormones. Recent studies continue to support that migraine is precipitated by drops in estrogen concentrations, and minimizing this decline may prevent these headaches. The role of female sex hormone in migraine is continuing to unfold. We believe that our results may be of considerable practical value in informing the pregnant migraine sufferer about the prospects in pregnancy, postpartum period, perimenopause and menopause. Also, our data may be of theoretical interest for understanding the influence of sex hormones in general and particular among migrainuers.

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REFERENCES

1. Cupini LM, Matteis M, Troisi E, Calabresi P, Bernardi G, Silvestrini M. Sex-hormone-related events in migrainous females. A clinical comparative study between migraine with aura and migraine without aura. Cephalalgia. 1995; 15(2):140–144. doi: 10.1046/j.1468-2982.1995.015002140.x. [PubMed] [Cross Ref]
2. Granella F, Sances G, Pucci E, Nappi RE, Ghiotto N, Napp G. Migraine with aura and reproductive life events: a case control study. Cephalalgia. 2000; 20(8):701–707. [PubMed]
3. Granella F, Sances G, Zanferrari C, Costa A, Martignoni E, Manzoni GC. Migraine without aura and reproductive life events: a clinical epidemiological study in 1300 women. Headache. 1993;33(7):385–389. doi: 10.1111/j.1526-4610.1993.hed3307385.x. [PubMed] [Cross Ref]
4. Lance JW, Anthony M. Some clinical aspects of migraine. A prospective survey of 500 patients. Arch Neurol. 1966;15(4):356–361. [PubMed]
5. Maggioni F, Alessi C, Maggino T, Zanchin G. Headache during pregnancy. Cephalalgia. 1997; 17(7):765–769. doi: 10.1046/j.1468-2982.1997.1707765.x. [PubMed] [Cross Ref]
6. Mattsson P. Hormonal factors in migraine: a population-based study of women aged 40 to 74 years. Headache. 2003;43(1):27–35. doi: 10.1046/j.1526-4610.2003.03005.x. [PubMed] [Cross Ref]
7. Melhado E, Maciel JA, Jr, Guerreiro CA. Headaches during pregnancy in women with a prior history of menstrual headaches. Arq Neuropsiquiatr. 2005;63(4):934–940. doi: 10.1590/S0004-282X2005000600006.[PubMed] [Cross Ref]
8. Rasmussen BK. Migraine and tension-type headache in a general population: precipitating factors, female hormones, sleep pattern and relation to lifestyle. Pain. 1993;53(1):65–72. doi: 10.1016/0304-3959(93)90057-V. [PubMed] [Cross Ref]
9. Ratinahirana H, Darbois Y, Bousser M. Migraine and pregnancy: a prospective study in 703 women after delivery. Neurology. 1990;40(Suppl 1):437.
10. Sances G, Granella F, Nappi RE, Fignon A, Ghiotto N, Polatti F, Nappi G. Course of migraine during pregnancy and postpartum: a prospective study. Cephalalgia. 2003; 23(3):197–205. doi: 10.1046/j.1468-2982.2003.00480.x. [PubMed] [Cross Ref]
11. Scharff L, Marcus DA, Turk DC. Headache during pregnancy and in the postpartum: a prospective study. Headache. 1997; 37(4):203–210. doi: 10.1046/j.1526-4610.1997.3704203.x. [PubMed] [Cross Ref]
12. Somerville BW. A study of migraine in pregnancy. Neurology. 1972; 22(8):824–828. [PubMed]
13. Sanchez SE, Qiu C, Williams MA, Lam N, Sorensen TK. Headaches and migraines re associated with an increased risk of preeclampsia in Peruvian women. Am J Hypertens. 2008; 21(3):360–364. doi: 10.1038/ajh.2007.46. [PubMed] [Cross Ref]
14. Aegidius K, Zwart JA, Hagen K, Stovner L. The effect of pregnancy and parity on headache prevalence: the Head-HUNT study. Headache. 2009; 49(6):851–859. doi: 10.1111/j.1526-4610.2009.01438.x. [PubMed] [Cross Ref]
15. Marcus DA, Scharff L, Turk D. Longitudinal prospective study of headache during pregnancy and postpartum. Headache. 1999; 39(9):625–632. doi: 10.1046/j.1526-4610.1999.3909625.x. [PubMed][Cross Ref]
16. Aube M. Migraine in pregnancy. Neurology. 1999; 53(4 Suppl 1):S26–S28. [PubMed]
17. Natoli etal.2010
18. Google books 2010
19. Migraine: Diagnosis and management- Giles Erington

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