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# Relationship between cerebrovascular disease and use of oral contraceptive agents

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# RELATIONSHIP BETWEEN CEREBROVASCULAR DISEASE AND USE OF ORAL CONTRACEPTIVE AGENTS

By

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It is estimated that in 1961, oral contraceptive agents were employed by 408,000 women; in 1965, by 5,000,000; and that by 1980, twenty to forty million females will control their fertility with oral contraceptive agents. Never before has such potent medication been taken voluntarily by so many people for an object other than control of disease.(1)

Certainly today, these agents represent the least expensive, easiest and most certain method of contraception yet devised, but they are not wrought without hazard.

Since 1961, when the first case was reported, there has been growing interest regarding the relationship between thrombosis and oral contraceptive agents. The world literature has experienced a wide ranging controversy over whether this is either an effect and cause relationship, or a relationship due only to coincidence.

This presentation is limited to a comprehensive but succinct review in the world literature of: The 50-plus reported cases which show a relationship between cerebrovascular disease and the use of oral contraceptive agents; Hemostatic alterations, noted in conjunction with the use of oral contraceptive agents, which alledgedly fulfill the requirements of Virchow's triade for the pathogenesis of venous thrombosis: Various studies that evaluate the relationship between oral contraceptives and thromboembolic disease; and Contraindications to the use of oral contraceptive agents with regards to their relationship to cerebrovascular disease.

Insert 1

| | Outcome | Final diagnosis |
|---|---|---|
| omplete neurologic examination the same which revealed no residual paralysis or rologic disease<br>ormal EEG few days later | Discontinued contraceptive medication and no re-currance | |
| was followed with an EEG which showed tumor | Discontinued contraceptive medication-no recurrance | |
| ormal skull films<br>ormal CSF examination | 1)Suffered a major motor seizure<br>2)Developed Cheyne-Stokes respirations and a supraventricular tachycardia<br>3)Left pupil became fixed and dilated and she died shortly after | Post Mortum<br>1)Thrombosis of left internal carotid artery extending into the anterior and middle cerebral arteries<br>2)Swelling and softening of left cerebral hemisphere |
| Normal skull films<br>Normal CSF examination<br>EEG -slow wave focus, centering on left mporal region<br>Brain scan increased uptake in left ontal temporal and parietal areas<br>Left carotid arteriogram - complete clusion of left middle cerebral artery its origin | Slow improvement in asphasia and hemiplegia | |
| Normal skull films<br>CSF protein of 100 mg% | 1)No change for 24 hours<br>2)Rapidly deteriorated with signs of increasing intracranial pressure<br>3)Died | Autopsy<br>1)Cerebral infarct of left hemisphere<br>2)Thrombus that occluded left middle cerebral artery |

| Author | Oral Contraceptives | Age | Past and family history | Symptoms and signs |
|---|---|---|---|---|
| (2) Whyte | Ortho-Novum 2mg. for 2 years | 32 | Para 7. Patient was tired following shopping | Transient hemiparesis and aphasia for 10-15 minutes |
| (3) Hoogewerf | Oracon<br>C-Quens<br>Oracon or C-Quens | | No past migraine | Unilateral paresthesia followed by transient hemiparesis of varying degree, associated with severe headache. One suffered aphasia |
| (4) Wolf | Enovid 2.5 mg. for 1 year | 32 | 1)Rheumatic fever as a child with subsequent murmur or heart disease<br>2)Patient's mother suffered a "stroke" at 68 | 1)Patient found on floor attempting to reach a phone<br>2)Right hemiplegia, Babinski sign and homonymous hemianopsia<br>3)Unable to speak or write<br>4)Answers questions by nodding head |
| | Enovid 5mg for 4 years | 29 | Occasional diffuse headaches associated with spots before eyes | 1)Abrupt onset of right hemiplegia<br>2)Right facial weakness and Babinski<br>3) Expressive aphasia |
| (5) Bradford | Ovulen for 6 months | 23 | 1)6weeks prior to admission--transient diplopia<br>2)2 weeks prior to admission -- occasional headache | Sudden onset of:<br>1)Right upper motor-neuron paral si of face<br>2)Complete paralysis of right arm<br>3)Pronounced weakness of right leg<br>4)Aphasia |

Insert 2

| Tests | Outcome | Final Diagnosis |
| --- | --- | --- |
| 1)BP 160/90<br>2)Normal skull films<br>3)EEG -- suggested a left hemisphere lesion compatible with vascular etiology | 1)Discontinued Enavid<br>2)Gradual improvement in speech, reading and writing | Left parietal lesion, probably due to cortical venous thrombosis |
| Arteriography -- partial occlusion of right middle cerebral artery | | |
| 1) Aortic arch angiogram -complete occlusion of right common carotid artery at the carotid siphon | | |
| Arteriography - complete occlusion of right internal carotid artery near origin | | |
| Cerebral angiography --complete left internal carotid occlusion just above bifurcation | | |

| Author | Oral Contraceptives | Age | Past and family history | Symptoms and signs |
|---|---|---|---|---|
| (6) Lorentz | Enavid 5 mg. QID for 3 months for dysmenorrhea | 41 | | 1)Difficulty finding words for 12 hours<br>2)Headache for 12 hours<br>3)Nominal aphasia<br>4)Dysgraphia and dyslexia<br>5)Finger agnosia<br>6)Right-left disorientation |
| (7) Illis | ? for 2 months | 28 | 1)5 miscarriages<br>2)Occasionally hypertensive<br>3)Father with coronary artery disease<br>4)Paternal grandmother with hypertension | 1)Minimal left hemiparesis for 2 years following oral contraceptives<br>2)Left visual field disturbances for 2 years following oral contraceptives |
| | Ovulen for 9 days | 41 | 1)3 years previously, 5 weeks post-partum, episode of sudden onset of pain and cyanosis of right forearm, with absence of right brachial and radial pulses for 2 days | 1)Sudden onset of right sided headache and a complete left hemiplegia, hemianopsia and hemi-anesthesia |
| | Anovlar | 39 | 1)Sister with hypertension<br>2)Father died of heart disease<br>3)Occlusion of left anterior and posterior tibial arteries at age 30 | 1)After being on oral contraceptives:<br>a)Few weeks--attacks of clumsiness of left hand for 30 seconds every 2-3 days<br>b)2 months later: more prolonged episode that spread to involve left face, arm and leg<br>2)Left hemiparesis |
| | Conovid E for 5 months | 24 | | 1)Episodes of weakness of right body for 4 months<br>2)Dysphasia with last episode<br>3)Right face and arm weakness, nominal dysphasia and right-left confusion |

Insert 3

| Tests | Outcome | Final Diagnosis |
| --- | --- | --- |
| 1)Normal brain scan<br>2)Normal CSF examination<br>3)EEG-suggested bilateral cortical damage of diencephalic change | Persistent left hemiparesis after 5 months | Medial inferior pontine infarct |
| 1)Normal brain scan<br>2)Blood studies --moderately increased euglobulin lysis time<br>3)EEG-some asymmetry of slow activity with higher amplitude slowing over the left hemisphere and several bursts of asymmetric sleep spindles and vertex waves | 1)Questionable left facial paresis after 7 months<br>2)Discontinued contraceptive medication | Infarction (embolic?) in distribution of right middle cerebral artery |

| Author (8) | Oral Contraceptive | Age | Past and Family history | Symptoms and signs |
|---|---|---|---|---|
| Cole | Enovid 2.5 mg for 6 months | 24 | 1)Gravida 3, Para 3<br>2)Hypertensive with first pregnancy<br>3)Family history of hypertension | 1)After on Enovid:<br>a)4months-nausea and vomiting, vertigo, blurring of vision, diplopia for 30 minutes for three days<br>b)6 months-buzzing in right ear, vertigo, nausea and vomiting, headache and parasthesias in upper right extremity - weakness of left arm the next day<br>2)Right pupil 6mm; Left 4.5 mm<br>3)Mild right peripheral facial paresis<br>4)20-30% decrease in muscle power of both left extremities<br>5)Deep tendon reflexes slightly increased on left<br>6)Left plantar response more extensor than right |
| | Norlutin for 1 year | 24 | 1)Gravida 2, Para 2<br>2)Occasional syncope with menstruation | 1)Suddenly lost consciousness and noted improperly functioning left upper extremity<br>2)Opticokinetic nystagmus reduced in left to right target direction<br>3)Decreased sensation over left face<br>4)Moderate left central facial paresis<br>5)Tongue deviated to left<br>6)Muscle power in left arm was zero, in left lower extremity 60% of normal proximally and 80% distally<br>7)Left plantar response extensor, right flexor<br>8) Impaired position sense in left upper extremity, but not in lower<br>9)Extinction of pinprick in left limbs<br>10)Left visual field deficit with double simultaneous stimulation |

| Tests | Outcome | Final diagnosis |
| --- | --- | --- |
| Left retrograde brachial arteriogram showed an occlusion of the left vertebral artery in its turn on the atlas | Remained in a neurologic state and was discharged to a chronic nursing facility | Probable pontine infarction due to vertebral artery occlusion |
| Normal brain scan. CSF with protein of 95. EEG revealed 3-4 cycle/sec waves of 50 to 100uv in right anterior temporal mid-temporal region | After 8 months:very minimal left facial weakness | Infarction (embolic) in the distribution of right middle cerebral artery |

| Author | Oral Contraceptive | Age | Past and family history | Symptoms and signs |
|---|---|---|---|---|
| | Norethynodrel with Mestranol for 3 years | 33 | Treated with Reserpine for 2 years for hypertension | 1)Intermittent episodes of syncope, vertigo, and loss of balance for 3 weeks<br>2)Progress weakness of left lower extremity for 4 days<br>3)Admitted with a right hemiparesis<br>4)Neurologic examination revealed marked dysarthria; bilaterally decreased facial sensation; right central facial weakness and decreased gag reflex on right; tongue deviated to right; right hemiparesis and some ataxia of left extremities; plantar response extensor on right and flexor on left, with a hemisensory deficit on right limbs<br>5)Patient then developed bilateral extensor plantar response, stupor, disconjugate eye movements, and bilateral internuclear opthalmophegia and left peripheral facial palsy |
| | Ortho-Novum 2mg for 11 days | 37 | History of migraine headache since puberty. Cytomel 2.5ug/day for 2 years | 1)Right supra-orbital pain and sudden onset of a left hemiparesis affecting arm, leg and face<br>2)30 minutes later, she developed deviation of right eye towards the right for 15 minutes<br>3)Left limb muscle strength 60% of normal; left plantar response was extensor and right, flexor |

Insert 5

| Tests | Outcome | Final diagnosis |
| --- | --- | --- |
| 1)Decreased blood viscosity<br>2)Normal CSF examination, brain scan and central retinal artery pressures<br>3)Normal coagulation bleeding and prothrombin times | Neurologic deficit unchanged after 3 weeks | Infarction in the distribution of right middle cerebral artery (right posterior cerebral artery?) |
| 1)Normal lumbar puncture<br>2)EEG showed abnormal bursts of slowing over left hemisphere<br>3)Brain scans revealed a large area of abnormal uptake in left frontal parietal region<br>4)Previous left carotid arterigram showed constriction of left internal carotid artery as it entered the skull<br>5)Repeat left carotid arteriogram revealed no filling of anterior of middle cerebral arteries | Stopped medication and she became well in 1 day | Progressive occlusion of left internal carotid artery at the siphon |

| Author | Oral Contraceptive | Age | Past and family history | Symptoms and signs |
|---|---|---|---|---|
| | Norethindrone with Mestranol 2 mg for 5 months | 26 | Cardiac murmur | 1)Became nauseated, vomited and noted she could not see well in left visual field<br>2)Later, noted some parasthesias of left arm, leg and neck<br>3)Dense left homonymous hemianopia |
| | Norethynodrel with Mestranol for 1½ years | 29 | | 1)Progressive weakness of right arm over several weeks<br>2)Right lower extremity became affected and mental impairment became obvious<br>3)Memory impairment and dysphasia<br>4)Right hemiparesis and hemisensory deficit<br>5)Increased deep tendon refelexes and a right extensor plantar response |
| (9)<br>Holbrook | | 29 | | 1)May 1963, patient was given hormone tablets (?) to help her conceive. After 2 weeks she fainted, was asphasic and blind for 2 days, and had a severe frontal headache. Past history of frontal headaches<br>Improved after medications were stopped<br>2)Oct. 1966, patient was supplied with an oral contraceptive. On 10th day she fainted 3 times, became dysarthric and then aphasic. Blurring of vision, numbness, and weakness of right hand and arm, severe frontal headaches and sharp stabbing occipital region pain followed<br>3)December 1966, patient supplied with different oral contraceptive. On March 26,1966, she felt dizzy and faint, numbness and weakness developed in right arm and hand; became dysarthric and then aphasic. She had a severe frontal headache and sharp stabbing occipital pain |

| Tests | Outcome | Final diagnosis |
| --- | --- | --- |
| 1)Right carotid arteriography-no abnormality<br>2)Left carotid arteriography-middle cerebral branch occlusion | | |
| Arteriography showed narrowing of whole of left carotid tree | Remains considerably disabled | |
| | Good functional recovery, but exaggeration of right reflexes after 3 weeks | |
| | Discontinued oral contraceptive and she has remained well | |
| 1)Normal CSF examination<br>2)Right carotid arteriogram suggested vertebral insufficiency<br>3)Catheter studies suggested left vertebral artery was anomalous at origin<br>4)Right vertebral artery showed tapering and final and complete occlusion high in neck | Died | Autopsy-thrombosis of right vertebral artery with infarction of right brain stem |

| Author | Oral Contraceptive | Age | Past and family history | Symptoms and signs |
|---|---|---|---|---|
| Bickerstaff and Holmes (10) | | 34 | 1)4 months after starting oral contraceptive, she suddenly developed paralysis of left face and arm together with a right Horner's syndrome. Partial recovery followed. Patient refused to discontinue oral contraceptive. 2)6months later she abruptly developed aphasia, right sided hemianopia and paralysis of right arm. Partial recovery after 1 week, but showed pseudobulbar features with forced laughter and crying | |
| | | 33 | 1)Past history of diastolic hypertension | 1)3 weeks prior to admission, she developed weakness of right arm and leg for 2 hours and recovered completely 2)7 days later she developed a total right sided paralysis and aphasia which gradually cleared |
| | For 9 months | 23 | | 1)Sudden onset of momentary left temporal pain followed by jargon dysphasia, right hemiplegia, and loss of sensation over right face, tongue and arm. Symptoms lasted 24 hours |
| | For 12 months | 24 | | 1)Suddenly developed loss of sensation over right face and arm and jargon dysphasia Lasted 48 hours and then cleared 2)3 months and 4 months later (still on oral contraceptive), she had an identical, though shorter, attack and recovered |
| | For 6 months | 26 | | 1)Sudden onset of pain in right neck followed by numbness of right face and parasthesias down left side of body, accompanied by distortion of hearing, double vision, slurring of speech and hiccups 2)Paralysis of right 6th and 7th |

Insert 7

| Tests | Outcome | Final diagnosis |
| --- | --- | --- |
| | All features cleared over two months | |
| | Lasted 7 days and then rapidly recovered with residual increase in right sided reflexes | |
| | Steady recovery over 6 weeks | |

| Author (continued) | Oral Contraceptive | Age | Past and Family history | Signs and symptoms |
|---|---|---|---|---|
| | | | | cranial nerves<br>3)4 hours later a left hemiplegia occured, followed by tetraplegia and deep coma<br>4)Consciousness returned, but she was anarthric,tetraplegic and subject to decerebrate attacks on stimulation |
| | Two types for 14 months | 32 | Suddenly developed flaccid paralysis of right face and arm with aphasia | |
| | Several months | 27 | 1)3 weeks previously, sudden paralysis of right face, arm and leg which resolved after 3-4 days<br>2)Examination showed a right upper motor neuron facial weakness and an increase in right arm and leg reflexes | |
| | 5 months | 36 | Suddenly developed a right hemiplegia and dysphasia | |
| | 1 year | 31 | | 1)Abrupt onset of vertigo, vomiting and ataxia of gait accompanied by marked course tremor of head, arms and legs of the type seen in lesio of red nucleus. Marked emotional lability. Eye movements showed spontaneous irregular vertical nystagmus; also a coarse static tremor of all limbs increased by movement. Abnormal left plantar reflex |

| Tests | Outcome | Final diagnosis |
| --- | --- | --- |
| | After 2 months, mild weakness of left side with hyperreflexia and sensory loss | |
| Right carotid arteriography-total occlusion of right middle cerebral artery | | |
| | After 3 weeks, increase of right sided reflexes only | |
| Normal CSF examination | Considerable disability after 6 months | |
| Normal CSF examination at onset | After 3 months, residual expressive and receptive dysphasia with increase of right sided reflexes | |
| | After 2 months, gross disability and marked expressive dysphasia | |

| Author | Oral Contraceptive | Age | Past and family history | Symptoms and signs |
|---|---|---|---|---|
| | 2 years | 31 | | 1)Sudden onset of distortion of sensation in the occipital region and this area became hyperasthetic. Ptosis of right eyelid, diplopia and a left hemiparesis with loss of sensation followed<br>2)Symptoms remained for 5 days and gradually improved |
| | 18 months | 36 | Migraine attacks associated with headache and vomiting for 15 years | 1)Abrupt onset of weakness of left face, arm and foot with some weakness of thigh<br>2)Left sided hyperreflexia and an extensor plantar |
| | 9 months | 35 | 1)Awoke with right sided hemiplegia and aphasia<br>2)Speech returned after 3 days and limbs became normal after 7 days | |
| | 1 year | 38 | Past history of hypertension | Suddenly developed paralysis of right side of body with dysphasia |
| | 1 year | 45 | | Suddenly developed tingling throughout right side of body, accompanied by a brief period of confusion and prolonged dysphasia |
| | 18 months but had stopped shortly before onset of symptoms | 33 | | Right hemiplegia and aphasia occured suddenly |

| Author | Oral Contraceptive | Age | Past and family history | Symptoms and signs |
|---|---|---|---|---|
| | 1 year | 30 | 1)Several episodes of flashing lights and impairment of both visual fields with occasional headaches while taking oral contraceptive<br>2)Twice suddenly fell to ground, once with vertigo<br>3)Refused to stop the "pill" and these transient ischemic attacks of brain stem continued<br>4)After 3 months, she agreed to stop oral contraceptive and died 2 days later | |
| | 9 months | 30 | 1)Suddenly developed vertigo and tinnitus in left ear<br>2)10 days later, sudden vomiting was followed by vertigo and ataxia, which lasted 24 hours and then ceased.<br>3)Patient left with left sided cerebellar ataxia for 3 weeks and then gradually improved | |
| | 2 years | 41 | 1)Suddenly developed blurred vision followed by total blindness, vertigo and ataxia<br>2)Total blindness for 24 hours, followed by partial recovery, leaving her with a persistent macula-sparing congruous left homonymous hemianopia | |

Insert 9

| Tests | Outcome | Final diagnosis |
| --- | --- | --- |
| | | Autopsy - no structural cause for death |
| CSF was normal | | |
| CSF was normal | | |

| Author | Oral Contrapeptive | Age | Past and family history | Symptoms and signs |
|---|---|---|---|---|
| Baines (11) | Conovid for 2 weeks | 29 | | 1)Sudden onset of vomiting and convulsions followed by flaccidness<br>2)Right hemiplegia with sustained ankle clonus and increased tendon jerks<br>3)Comatose with right sided Babinski and Hoffmann |
| Zilkha (12) | Enavid for 7 weeks | 23 | | 1)Unusual feeling and sensation of falling for 15 minutes - twice, followed by confusion, dysphasia, disorientation and difficulty naming objects<br>2)Weakness of right face and hand<br>3)Increased deep tendon reflexes in right arm |
| | Ortho-novin 2mg for 6 months | 26 | Epileptic seizures at age 17; none since age 19 | Congruous left upper quadrantic visual field defect for 6 weeks |
| Stewart-Wallace (13) | Conovid E for 22 months | 32 | | Suddenly developed a typical lateral medullary syndrome, with severe vertigo and vomiting, ataxia, diplopia and right Horner's syndrome, and loss of sensation over right face and left half of body |
| | Ovulen for 6 months | 46 | History of migraine since childhood associated with patchy vision, numbness of lips and arms followed by headache | Sudden onset of vertigo and unsteadiness, causing her to lurch and fall to the right, visual discomfort on looking to the right without closing one eye, and excessive drowsiness. Both plantars were extensor. |

Insert 10

| Tests | Outcome | Final diagnosis |
| --- | --- | --- |
| 1)CSF was normal<br>2)Skull films were normal<br>3)EEG -- local excess of delta activity in left central region | | Autopsy-Thrombosis of left middle cerebral artery and thrombosis of right anterior cerebral artery |
| 1)Normal CSF<br>2)Normal skull films<br>3)Normal left carotid arteriogram<br>4)Normal lumbar air encephalogram<br>5)EEG showed delta activity at $2\frac{1}{2}$/sec in left fronto-temporal area | After 4 weeks, nominal dysphasia | |
| | No change after 4 months. Stopped oral contraceptive | |
| | Slight residual defect after 2 months | Thrombosis of vertebral of a posterior inferior cerebellar artery |
| | Gradually recovered | Ischemic disturbance of brain stem |

| Tests | Outcome | Final diagnosis |
| --- | --- | --- |
| 1)WBC of 18,100/cmm<br>2)ESR of 45mm per one hour<br>3)Increased total fatty acids and serum cholesterol<br>4)Left carotid angiogram complete occlusion of internal carotid artery at origin | | Autopsy - recent infarct of left cerebral hemisphere associated with edema and uncal herniation; thrombosis of left common carotid, left middle and anterior cerebral arteries |
| 1)CSF with 6 rbc/cmm<br>2)Angiography-block of lower part of basilar artery | | Autopsy -thrombus of last inch of right vertebral artery and softening of right pons |

| Author | Oral Contraceptive | Age | Past and family history | Symptoms and signs |
|---|---|---|---|---|
| (14) Nevin | Norethisterone and Ethinyioestradiol for 1 year | | Mild pharyngitis 5 days prior to admission | 1)On day of admission, she felt cold, became restless, and confused and unable to move right arm and leg<br>2)Drowsy with slurred speech; right pupil slightly larger th left; upper motor neuron weakn of right face; right hemiplegi and tenderness over left common carotid artery |
| (15) Ehtish-Amuddin | Anovlar 4 mg for 6 months | 26 | | 1)Sudden onset of headache over the vertex, followed by pain in right side of neck, numbness of right face, sensation of coldness in right halves of lips, giddiness, ataxia, syncope, diplopia, hyperacusis in both ears and parasthesias in left arm and leg.<br>2)Paralysis of right lateral rectus, lower motor neuron weakness of right face. Decreased left corneal reflex and decreased sensation over left face. Decreased hearing on right and Weber lateralized to left.<br>3)Weakness of left arm with slightly increased tone. Left hemi-hypalgesia. Increased deep tendon reflexes on left. Left plantar was extensor and right, equivocal.<br>4)Developed left hemiplegia, dysarthria and unconsciousness; associated with increase in tone and opisthotonos; both plantars became extensor<br>5)developed a spastic tetraple |

| Tests | Outcome | Final Diagnosis |
| --- | --- | --- |
| 1)Normal CSF<br>2)EEG - delta focus over posterior right hemisphere<br>3)Brain scan--abnormal density along distribution of right middle cerebral artery<br>4)Angiography - total occlusion of right middle cerebral artery | Almost full recovery in 3 weeks | Right middle cerebral artery stem occlusion with infarction of right cerebral hemisphere |

| Author | Oral Contraceptive | Age | Past and family history | Symptoms and signs |
|---|---|---|---|---|
| (16) Gardner | 6 women aged 22-39 on oral contraceptive up to 14 months | | Non-contributory | All experienced a prodrome of recurrent vascular headache lasting several weeks. In 5, this represented a new headache pattern. In 5 patients cerebral infarction occured. In 4 of these, the lesion developed after days of transient focal symptoms. In one, recurrent episodes of crural monoparesis occured at intervals preceeding hemiplegia. The fifth patient became paralyzed abruptly. The last patient developed cerebral migraine with left sided numbness and had a generalized seizure. All patients terminated oral contraceptives with onset of neurologic symptom, except the last patient. Carotid arteriography in one patient 3 weeks after onset of aphasia disclosed segmental narrowing of occlusion of smaller cerebral arteries |
| (17) Shafey | Enovid 10mg for 3 years | 29 | Past history of hypertension | 1)Developed occipital and frontal headaches and transient episodes of vertigo, diplopia and numbness of right hand. Noted to be confused and disoriented and unable to remember events. Headaches increased in severity, were unremitting and localized in right parietal region. 2)Demonstrated left hemiparesis, left hemihypalgesia and dense left homonymous hemianopsia with decreased optokinetic nystagmus on moving the tape to the right. |

| Tests | Outcome | Final diagnosis |
| --- | --- | --- |
| 1)Normal CSF<br>2)EEG-delta focus over right temporocentral region<br>3)Brain scan-abnormal pickup over same area<br>4)Right carotid angiography showed beading of right middle cerebral artery and occlusion of several major Sylvian branches. 5mm shift of right internal cerebral vein to left | Left spastic hemiparesis after 1 month | Large infarction in right cerebral hemisphere due to partial occlusion of right middle cerebral artery |
| | Resolution of all neurologic signs over 1 week | Sensory stroke due to thalamic infarction |
| 1)Angiography and pneumoencephalography revealed no abnormalities<br>2)Brain scan- abnormal pickup in right parietal region | Rapid improvement in a few days | Infarction in right parietal region |
| 1)Normal CSF<br>2)EEG-delta focus in right frontotemporal region<br>3)Brain scan - pickup along distribution of right middle cerebral artery<br>4)Carotid angiography - narrowing of intracranial portion of internal carotid which appeared beaded and diffuse | Retained a spastic hemiparesis | Right hemisphere infarction in distribution of right middle cerebral artery |

| Author | Oral Contraceptive | Age | Past and family history | Symptoms and signs |
|---|---|---|---|---|
| | Norinyl 2mg for 4 months | 20 | | 1)Began to have right sided headaches and suddenly became hemiplegic<br>2)Flaccid left hemiplegia with weakness of lower left face, left hemihypalgesia and left homonymous visual field defect |
| | Enovid 5mg for 2 years and Norlestrin 5 mg | | 1)Family history of Raynaud's phenomenon of strokes<br>2)Thrombi of left radial and ulnar arteries, gangrene of left finger tips and amputation of left hand | 1)Gradually progressive numbness of left side of body and face.<br>2) Examination revealed left homonymous hemianopsia and left hemihypalgesia |
| | Ortho-Novum 10mg for 2 years | 39 | Past history of hypertension, obesity and abnormal glucose tolerance | 1)Became irritable and noted right sided headaches. Followed by parasthesia of left hand, arm and face<br>2)Examination revealed constructional apraxia, right to left confusion and left homonymous hemianopsia |
| | Enovid 5mg for 6 months | 28 | | 1)2 days following a cholecystect patient noted headache and became periplegic<br>2)On examination she had a dense left hemiparesis, homonymous heimianopsia and hemihypalgesia |

Insert 14

| Tests | Outcome | Final diagnosis |
| --- | --- | --- |
| 1)Bilateral carotid angiograms showed a left temporoparietal mass and beading of right interal carotid artery intracranially and its proximal branches; suggestion of superior sagithal sinus thrombosis<br>2)CSF grossly bloody with xanthochromic supernatant | | Autopsy-intra-cerebral hematomia in left fronto-temporal regions; multiple infarctions in both hemi-spheres; thrombosis of superior sagittal sinus and cortical veins. |
| 1)Normal neurologic examination several years later | No recurrance | |
| 1)Neurologic examination was unremarkable | Discontinued oral contra-ceptives and no recurrance | |
| 1)Neurologic examination was unremarkable | No recurrance | |
| 1)Neurologic examination was unremarkable | No recurrance | |

| Author | Oral Contraceptive | Age | Past and family history | Symptoms and signs |
|---|---|---|---|---|
| | Ortho-Novum 10mg for 1 year | 29 | Marfan's syndrome | 1)Onset of headaches followed by stiff neck, nausea, vomiting, confusion, disorientation, and generalized seizures with focal onset in right arm<br>2)Examination revealed expressive dysphasia, right hemiparesis and bilateral extensor plantar responses. Her neck was stiff and there was a positive Brudzinski sign |
| (18)<br>R.H. Messer (unpublished) | 2 months | 32 | 1)Inability to become pregnant<br>2)Hypothroid with PBI of 2.9 | 1)Patient discontinued oral contraceptive after temporarily experienc an acute loss of vision, vertigo, aphasia and weakness and numbness of left arm |
| | Norethindrone 2mg and Mestranol .1mg for 3 months | 21 | | 1)Onset of retro-optic headache that was progressive; suddenly associated numbness of left hand and arm. Symptoms were transitory and cleared in 24 hours |
| | Norethindrone 2mg and Mestranol .1mg for 7 months | 20 | | 1)Pain in left calf for 3 days followed by bilateral loss of vision in the right side which was temporary in nature and cleared spontaneously |
| | Norethindrone 2mg. and Mestranol .1mg for 1 month | 20 | | 1)Episode of partial loss of vision in one eye that was temporary and cleared spontaneously |

Insert 15

| Tests | Outcome | Final diagnosis |
| --- | --- | --- |
| 1)Unremarkable neurologic examination | No recurrance | |

| Author | Oral Contraceptive | Age | Past and family history | Signs and symptoms |
|---|---|---|---|---|
| | Norethindrone 5 mg for 1 week | 27 | 1)Previous hysterectomy<br>2)Lens opacity in left eye since birth | 1)Patient received oral contraceptive as a trial for symptomatic relief of chronic mastitis of both breasts<br>2)Patient noted vertigo, confusion and a syncopal episode for first time in her life after 1 week |

Patterns that evolve from the cases presented are that one fourth of the women had a past or family history that could be related to their cerebrovascular disease; that the cerebral arteries were frequently the site of involvement; and that initially, many of the neurologic symptoms were transient or slowly progressive. This last pattern should serve as a warning to patient and physician that the oral contraceptive must be stopped immediately.. No other trend is noted with regards to patient's age, signs and symptoms, actual diagnosis or type dosage or duration of use of oral contraceptive, other than perhaps the incomplete nature of pertinent information presented.

> "Find out the cause of this effect,
> or rather say, the cause of this defect,
> For this effect defective comes by cause."
> Hamlet Act I,Scene5 line 97

With this in mind, we examine the vascular and hematologic alterations brought about by oral contraceptive agents. It has been noted the oral contraceptives, as well as pregnancy, result in a loss of venous tone, venous distension with an associated decrease in velocity of blood flow through veins.(19) This would promote stasis, which is a portion of Virchow's triade for the pathogenesis of a thrombus.

In rabbits treated with Enovid, changes were produced that were similiar to those found in the vasculature of pregnant rabbits. These included an increase in smooth muscle; a lacy and fragmented appearance in the reticulum; a decrease in the amount of Alcian-blue positive material; and the elastica became more attenuate and lost much of its corregation.(20) This would not meet Virchow's requirement of intimal damage for promotion of thrombus formation.

It is generally agreed that the following hematologic factors and elements are increased with the use of oral contraceptive agents: Fibrinogen, prothrombin, Factors VII and X, platelet count, profibrinolysin (plasminogen) and inhibitor (antifibrinolysin). The following Factors and tests are not increased with use of oral contraceptives: Factors V and VIII, 1 stage prothrombin time, partial thromboplastin time, Cephalin time and Fibrinolysin (plasmin). Even though several coagulation factors and elements of blood are increased, this does not truly represent a hypercoagulable state necessary for the pathogenesis of a thrombus as specified by Virchow. It is difficult to quantitate in vitro alterations in coagulation mechanisms with those in vivo, other than to say that coagulation will be delayed or will not take place in the absence of any of the coagulation factors. To find even a single in vitro increase in a clotting factor or substance and describe this as a hypercoagulable state, one must first correlate this with changes in other factors in vivo which may have a compensatory influence.

The contraindications for the use of oral contraceptives appear greater in number than are frequently stated. The contraindications enumerated below are incriminated because of their role in Virchow's triade for the pathogenesis of venous thrombosis:

1) Damage to the endothelium of the veins;

2) Increased coagulability of the blood;

3) Stasis of blood in the veins;

and its relationship, direct - Virchow's triade itself, or indirect-resultant emboli, to cerebrovascular disease.

A)Family history of:

1) Vascular disease

2) Coronary or ischemic heart disease

B) Previous history of:

1) Varicose veins

2) Thrombophlebitis

3) Thromboembolic disease and/or infarction

4) Rheumatic fever in childhood, but without evidence of cardiac sequelae (16)

5) Congestive heart failure

6) Coronary or ischemic heart disease

7) Vascular disease

C) Current history of:

1) Lactation (21)

2) Gross overweight (15)

3) Increased age (15)

4) Carcinoma (15)

5) Operation or other trauma

6) Polycythemia

7) Hematologic disorders associated with increased destruction of erythrocytes with subsequent release of thromboplastin: (22)

a) Sickle cell hemoglobinopathies

b) Paroxysmal nocturnal hemoglobinuria

c) Thrombocytopenic Purpura

d) Acquired hemolytic anemias

Until recently, the American literature has hinted that the relationship between cerebro-vascular disease and oral contraceptive agents was one of coincidence only, where-as the English and European literature has suggested an effect and cause relationship. However, the most recent American literature seems to have joined step with the British. On the basis of this knowledge, of the severe cerebrovascular lesions that do occur, of the hematologic and vascular alterations reported, of the numerous contraindications and on the basis of conservative medical judgment, it is felt that the relationship between cerebrovascular disease and oral contraceptive agents is a relationship of effect and cause.

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