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Extra-uterine gestation : with special reference to the tubal variety

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by

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INTRODUCTION

This paper is written to present a brief review of the current literature on ecchyesis. The older literature is used to develop the trend of thought and the manner in which things are done in 1942.

There is no original investigative work incorporated within the paper. All material has been gathered from the volumnous library of the University of Nebraska College of Medicine.

As indicated, the chief topic is extra-uterine pregnancy. This subject in itself is a tremendous one so it was deemed best to limit the paper to the tubal variety. Special references will be made to the other forms of extra-uterine gestation.

There is much controversial thought as concerns the subject, notably in the signs and symptoms, and diagnosis. Those sections have been given to show in their entirety the different opinions of various authors and the thought of the majority.

HISTORY

Extra-uterine pregnancy, ectopic pregnancy, or ecchyesis may be defined as that condition which arises when a fecundated ovum lodges and imbeds itself in any situation outside the uterine cavity, nidation proceeding in the aberrant site for a variable period (1).

Those who have spent much time reviewing the literature of the ancients find no allusions to this subject. There have been references made by some historians to the Talmud in which they say this lesion was described. However, "the first authentically recorded case is that of Albucasis, an Arabian physician, living in Spain, and flourishing about the middle of the eleventh century. He reports a case wherein he saw parts of a fetal body escaping from the abdomen of a woman by the process of suppuration. This case was of the old, long retained secondary abdominal type and all of the older reported cases were of this kind (1)".

Early in the sixteenth century there was reported by Cordaeus the lithopedian of Sens. The description of this phenomenon is published by Rousetti in Baughin's Gynecorum (1).

In compiling a history of this vast subject the writer is greatly indebted to Schumann who in turn has used freely the magnificent essay by Campbell published in Edinburgh in 1842. Further use of Parry's monograph published in 1876 is made for the historical study.

Following the lithopedian of Sens the next important step in recognizing such a condition as extra-uterine gestation was made with an observation by Cornax in the early half of the sixteenth century.

" In the early half of the sixteenth century Cornax dilated an ulcer which formed near the umbilicus, and extracted a semi-putrid fetus, which had been retained for nearly five years. When the patient arrived at the termination of her pregnancy, pains resembling those of labor supervened, and were followed by an unusual sound in the abdomen, but the uneasiness did not subside. For four years the abdomen continued distended and painful; and at last, a fetid discharge issued per vaginam. First one abscess, and thereafter another, formed at the umbilicus; these were dilated by an incision eight inches in length, and the fetus removed. The woman recovered so well after the operations so as to conceive again, and she had a natural delivery and died sometime thereafter. This case was considered by its narrator as one of rupture of the uterus; but as the pains continued after the unusual sounds in the abdomen were heard, and that there is no mention of there having been any hemorrhage, it should rather be viewed as an instance of extra-uterine gestation (1)."

About the time of Cornax' exploits there appeared the remarkable case of Jacob Nufer. Jacob Nufer was a swine spayer in Switzerland.

Although Nufer's case is recorded as the first cesarian section operation on the living woman there is no mention made as to whether or not the pregnancy was within or without the uterus.

Nufer's wife was a primipara. Labor came on and lasted for several days. During that length of time several mid-wives and lithotomists had gathered at the bedside, all unable to alleviate the sufferings of the woman. Nufer, possibly over zealous, approached his wife with the only means of saving her that seemed to him plausible. With the blessings of God, and the magistrate (a first instance of legality of such an operation), and the consent of his wife, he proceeded to lay open the abdomen as was his custom in spaying swine. His skill at his former trade allowed him to make an almost exact incision and extract a living baby boy. The child grew and lived to the unheard of age of seventy-seven years. Nufer's wife was later confined four times and bore one set of twins.

About 1540 an operation devised by Bain was performed for a long retained fetus. A woman called LaCavalla due to her great size, became pregnant in Italy. The fetus died and the soft parts sloughed through the vulva but the bony portions had been retained within her. She again became pregnant and the period of gestation was marked by a severe wasting of the tissues of the mother's body. Bain, a traveling surgeon, offered to restore this woman to health---

for a price of course. He opened the abdomen, peritoneum and uterus and extracted the skeleton of a fetus. The early use of antiseptics is here illustrated by the fact that before closing the wound the edges were washed with wine and caustics. The woman recovered and had four other children. This operation and the facts presented have been thought by Bovee (2) to represent a hysterectomy rather than an operation for the relief of an extra-uterine pregnancy.

About the time of Bain's case in the early sixteenth century there appeared a similar case reported by Etienne de Manial (3). The facts of this case are lacking.

The earliest absolutely definite case of surgical interference for the removal of the abdominal fetus is that of Primerose in 1594. "The history of this patient is classical. She was twice pregnant with extra-uterine children---first in 1591, and again sometime before 1594. The cyst of the first child opened spontaneously through the abdominal wall. The fistula was enlarged and this child extracted by Jacob Noierus, a surgeon. This operation proving successful Primerose removed the second infant by gastrotomy two months later. It is easy to imagine how he was led to perform the second and more hazardous operation (4)."

" A case that upon the whole, may be considered very characteristic, is related by Felix Platerus, 1594, in which the concubine of one of the sacerdotal order, at the close of her third pregnancy, endured for eight days pains resembling those of labor, which then subsided without, however, being followed by delivery. After having for sometime suffered from a variety of complaints, a small swelling, the size of an acorn, formed a little above the umbilicus; it was laid open, and an entire but semi-putrid fetus extracted from the abdomen; and the hand thereafter introduced into the cavity for the removal of any remaining portions of the decomposed mass. The patient was restored to health, and survived the operation a year (4)."

Little more is reported of extra-uterine pregnancy until almost a century later when the existence of definite forms of this lesion were first noted by Riolanus, the younger, who first described tubal pregnancy in his Anthropographia, which was published in 1649. He states, that in the year 1640, he recognized a tubal gestation in the body of a washerwoman in the service of Anne of Austria (4). The same writer according to Schumann noticed and reported such a case in 1604 and says this to be the first reported of its kind (1).

"In 1669 that master of obstetrics, Mariceau, reported a case of ruptured extra-uterine pregnancy. The text of his description being as

follows; 'History of a woman in whose abdomen there was found, after death, a small fetus about two and one-half inches long, together with a great quantity of coagulated blood. The history of this case deserves to be carefully examined into, to decide whether the fetus (as believed by many) was generated in the ejaculatory vessel, called the tube of the womb. On the sixth day of January, 1669, in the village of Gorrari, I saw in the hands of a chirurgus called Benedict Vassal, a uterus, the picture of which is shown at the end of this chapter, which the same chirurgus had a short time before removed from the body of a woman aged 32, who died after three whole days of torture with the most agonizing pains in the stomach, through which she had fallen into frequent fainting spells and the most violent convulsions. This woman had borne eleven children at term, but in her twelfth pregnancy, at about two and one-half months, the womb dilated in the direction of the right horn, and, unable to stand distension, ruptured. The fetus was cast out at once and found among the intestines of the mother, with a great quantity of coagulated blood in the whole lower abdomen. Many physicians, chirurgi and other students of nature did as we did ourselves, betook themselves to this chirurgus to see this uterus (which he showed for a prodigy), persuading them that it was formed in the ejaculatory vessel, which Fallopius calls the trumpet of the womb. They believed at once,

without anymore investigation, that this was just as the said chirurgus told them, and that this case confirmed stories of a like nature narrated by Riolanus. However, I examined the parts of that uterus most carefully and attentively, and it is known to me that those who had fallen into this opinion were in error whither the chirurgus was leading them, and for this reason, at that very time, I took a drawing of the womb as it was then, and this is the more faithful, true drawing than that which the chirurgus caused to be engraved on brass after an entire month, at a time when the uterus retained almost nothing of its primitive form, and was spoiled by the handling of a thousand men or more who had seen the uterus, pulled it, disturbed it, turned it inside out that they might examine it. Many have brought forward this case to prove to us that the testes (ovaries) of women are full of little ova, which, at the time of coitus, freeing themselves and emerging from the body proper of the testes (ovaries), are borne into the uterus through the tube, afterwards to serve for the generation of the fetus; and one of these so-called ova had by chance remained in the tube of this woman, instead of passing forward into the uterus, and that this was the cause of her death. Regnus Graaf among others holds this opinion, for the confirmation of which he brings forward the figure of this uterus, which he painted

from this case which the chirurgus of whom I have spoken had already given to the public; as one finds it on the 260th page of this book on the generative organs of women; but any who will, carefully and without prejudice, examine the following figure, which is most faithful and faultless, and at the same time examine into our reasons, will find that we have given another demonstration and that we believe that to be the true explanation. ' It was Mariceau's contention that generation in man was accomplished by the union of two liquids, the male and the female, and that accordingly these liquids only meet and cause fetal development in a large and suitable cavity, as that of the uterus. He held that tubal or ovarian pregnancy was impossible, and hence proved to his satisfaction that the case referred to was a pregnancy in the uterine horn. Study of the plate as presented by him merely enhances the confusion, since, while the rupture seems to have taken place in the ampulla of the tube, the location of the right broad ligament makes it evident that the gestation sac must be an elongated uterus and uterine cornua. The question, therefore, must perforce remain unsettled (1)."

According to Parry, all remained quiet on this front following Mariceau until about 1682. During this year there was published an article by M. de St. Maurice, who observed the first authentic case of

ovarian pregnancy. In his description Parry says that perhaps this man was not sufficiently informed or that he lacked sufficient knowledge to state clearly what he found, but from the writings and the report it must be considered that the pregnancy was ovarian and that since such cases had not previously been reported the odds are in the favor of the investigator (4).

The first case in which any report of the pathological anatomy of extra-uterine pregnancy was studied comes from France. It occurred in 1693. A woman had been condemned to death and while waiting for the executioner, had intercourse with a fellow prisoner. At the post-mortem the fimbria of the left tube were found to be dilated and a cyst was found measuring more than one inch in diameter. This portion was so tied to the ovary that separation of the tissues without injury to them was impossible. Therefore, no attempt at separation was made, however, from this time on more and more cases are recorded and various conclusions drawn, many of which present similar arguements to those exposed by Mariceau (4).

Pierre Dionis published the first clear and accurate understanding of the phenomonen, and cause of ecchyesis. He says, "if the egg be too big, or the tube too small in diameter, the egg stops and can get no further, but shoots forth and takes root there; and having the same circumstances and communication with the blood vessels of the tuba that it

would have had with those of the womb, had it fallen into it, is nourished and grows big to such a degree that the membranes of the tuba being capable of no such distension and dilatation as that of the uterus, breaks at last, and the fetus falls into the cavity of the abdomen, where it sometimes lies dead for many years, and at other times occaisions the death of the mother by breaking open its prison (1).

The history of treatment continues following Platerus example of operation and removal. Calvo, a Frenchman, operated in 1714 and removed a fetus. Thus, it can be seen that a relative dark age followed Platerus and his method of treatment.

" Mr. John Bard was a surgeon in New York, and we know of no one who operated in this country before him. The patient was a Mrs. Stagg, the wife of a mason, and the operation was performed several years before it was published, for Mr. Bard communicated an account of it to Dr. Fothergill, in a letter, which was dated on the 25th of December, 1759.

On January 14th, 1791, this operation was performed on this side of the Atlantic for the second time, the subject of it being a Mrs. Cooke, the wife of a Virginia planter. The operation which was done by Dr. William Baynham, a country physician, was entirely successful. The same gentleman operated with the same results upon a negro slave on February 6th, 1799. This was the fourth American gastrotomy for the removal of

an extra-uterine foetus. The third one was performed by McKnight, and communicated to the famous Dr. Lettsom, by Dr. Mease of Philadelphia, and published in 1795. Dr. Baynham's cases are well worth attentive study. They illustrate the intrepidity and good judgement so often displayed by the provinicial surgeon, who separated by long distances from his fellows, often has to act in the greatest emergencies without the counsel which he may earnestly desire. Almost a quarter of a century passed before the operation was repeated in this country. On the 6th day of October, 1823, it was again performed by Dr. Wisehart, likewise a country practitioner. The sixth American operation was performed on February 7th, 1846, by Dr. A.H. Stevens of New York, a man who had all the advantages of a metropolitan practice and experience (4)."

With the magnificent results reported by those few who had courage enough to attempt the operation of gastrotomy, interest in the subject of ecchyesis grew. More and more reports fill the literature. In 1824 Brechet added to the previously scarce literature what he thought to be a new type pregnancy. The so-called interstitial type. In 1837 Dezemeris published his monograph in which he made a new and complex arrangement of the varieties of this phenomenon. In 1842 Campbell published his memoirs which added greatly to the interest of the subject.

We now come to Parry and his classical pub-

lication. Parry wrote in 1875 and his work was published in 1876. Until this time there had been no concise, accurate record of the exacts things to be met while dealing with this sort of lesion. Parry set forth a series of etiological agents, signs and symptoms, and diagnostic points that today are very helpful in determining exactly what sort of pathological process exists in the patient. Schumann who wrote in 1921 has this to say of Parry's momentous work, " no better appreciation of the amazing advance in the knowledge of intrapelvic pathology, as well as the marvels achieved by modern surgery, can be obtained than by a close reading of Parry's book, published only a little less than five decades ago. In the light of routine hospital work of today, the facts brought out in this monograph seems to express the thought of 1476, rather than 1876; and to compare the results of treatment then and now must lead every reader to mentally add another star to the galaxy that crowns those two pioneers, to whose bold and scholarly efforts we owe all of the surgical wonders of our time, Pasteur and Lister.(4)". Whatever Schumann has to say of Parry he cannot detract from the magnificance of Parry's monograph. Schumann himself quotes directly from Parry in many places but of course not as to treatment. This is a good example of the pillar in the field of scchyesis that Parry created. We see in these two monographs (Parry and Schumann)

the great failure of the medical profession in its character---the ease and eagerness with which one practitioner condemns another instead of heralding him.

Following Parry the next great contribution came by Lawson Tait, who operated fifty-six cases with but one death. This would be quite a mark to establish in 1942. Tait reported in 1885.

Next, Warth in 1887, wrote a monograph in which is found the principle followed by the pathologist today in the examination of specimens of this lesion (1).

Since 1890 the literature has abounded with articels concerning ecchyesis. The surgical principles once established by Lister as concerns asepsis, have given rise to the almost unanimous approval for only one treatment of this condition---immediate laparotomy.

The twentieth century has contributed much new material for the diagnosis, symptoms and signs, and we are still in the realm of almost miraculous advances in the treatment as evidenced by the appearance of the sulfonamides for the control of infection, and the advent of plasma and plasma banks and new supportive principles for the treatment of shock.

Further reports of recent advances since Schumann's great work will be found incorporated within each section as a new topic is discussed.

ETIOLOGY

"---the human organism alone, from data obtainable, suffers from ectopic gestation with all its sequences and complications (5)."

In bringing about a logical, reasonable classification of the causes of extra-uterine gestation there must be an outline. It is found that each author who has written on this subject has a different and varied classification. Therefore, the very simple classification as set forth by Schumann will be followed with a few modifications.

1. Obstruction of the tubal lumen from without.

The Fallopian tubes are compressible structures composed of soft tissue. They are made up of a mucous membrane, muscle coat lying longitudinally and transversely, and an outer coating of fibrous tissue surrounded by peritoneum. In any case where there is compression of these soft structures obstruction of the lumen will result.

a. Adhesions.

Adhesions form resultant to an infection or inflammatory process around the tubes or within the tubes. When connective tissue ages it contracts. This is a cardinal pathological principle. Now, when infections are present and tissue destroyed, connective tissue is laid down without due regard to former spaces, tissues, etc. In such instances we find former separate tissues come to be bound together by this connective tissue, or adhesions. As these adhesions age they contract.

Such contraction may pull the tissues, including the tubes, into kinks and folds. The tubes may even be compressed directly by a circular band of fibrous tissue. Thus, may obstruction arise. Any inflammatory condition of the pelvis or abdomen may give rise to adhesions. Appendicitis, diverticulitis, peritonitis, urologic infections (cyctitis, ureteritis, pyelitis, etc.), even nephritis, have been named as specific causes (6). Many authors state that all true pelvic inflammations, or those serious enough to cause adhesions or kinking or compression of the tube, are initiated by an endosalpingitis (5), the infection spreading to the surrounding tissues of the tube by direct extension through the wall or by escaping through the open fimbriated end before closure of this structure takes place.

Brown (7) states that ectopic pregnancy may follow an attempt to determine tubal patency by the injection of gas or radio-opaque substances in sterility studies. His contention in that the gas or other injected substance causes an internal irritation of the tube, or that the tube was patent and the irritant material escapes into the peritoneal cavity by way of the fimbria, establishes an inflammation, and results in adhesions and loss of tubal patency.

b. Tumors, masses, and other conditions causing external pressure on the tube and thus closing the lumen.

This form of obstruction has been refudiated by many authors. This group would believe

that external pressure is purely coincidental with a previous inflammatory condition. However, Schumann (1) sites Gardner in a case which presented a large uterine fibroid coincidentally with an extra-uterine pregnancy. The pregnancy was found low in the pelvis under the fibroid. Macroscopically there was no indication of a previously existing inflammatory disease. Upon microscopic examination of the tubes and surrounding tissues there was no evidence of any inflammatory process either recent or old. Case reports are rare of this type obstruction and therefore it must be considered of rare occurrence.

Tumors of the wall of the tube, uterus, ovaries, colon, bladder, ureters, kidneys, etc., must all be considered as etiological possibilities not only by their mechanical obstruction but also by their irritative qualities.

2. Obstruction of the tubal lumen from within.

"---a tubal pregnancy is practically always preceded by an inflammatory reaction and in many cases by a period of sterility which, however, is only relative as the occurrence in nearly all of these cases of delayed pregnancy would denote (5)." Such was the opinion in 1908 and such is the most popular opinion in 1942.

It is today believed by the majority that an infection in the tubal lumen causes, by the process of repair and laying down of fibrous tissue, a narrowed lumen (7); an obstructed lumen due to exudate (8);

a kinked lumen; loss of cilia and their propulsion of the ovum toward the uterus; loss of muscular elements of the tubal wall and consequent loss of peristaltic movements of the tube.

Williams (5) theory is that an infection of the tube occurs. Following this infection there is repair by fibrous tissue. In this process many of the crypts in the mucosa of the tube may become bound together forming blind pouches or false diverticulae. He states that from ninety-five to ninety-eight per cent of all tubal pregnancies arise in this manner. These false diverticulae then recannalize, and by this process of healing and attempted restoration of the tubal lumen an ovum may fall into them and become fertilized. Unable to dislodge itself, the ovum establishes contact with the mucosa of the tube and thence grows too large to pass through the small lumen.

Mahfouz (9) believes that following an infection of the lumen of the tube there is a desquamation of the epithelium and subsequent loss of the cilia that provide the propulsion of the ovum to the uterus. He further believes that polypi growing from the tubal wall may impair the progress of the ovum. The ovum, as in Williams theory, becomes fertilized and grows too large to pass through the lumen.

Gonococci are the most frequent invaders of the tubes and are therefore considered to be the chief factors in producing strictures of these structures. However, any inflammatory process may produce

such a stricture. Streptococci, tubercle bacilli, colon bacilli, and many others have been shown by McGoogan and Collins in their lectures to be agents which may produce stricture and closure of the tubal lumina (10).

Associated with obstruction of the tubal lumina from within one must consider that pathological findings in the tubal wall itself may cause constriction. Some authors class this type pathology as producing the obstruction from without but there is marked evidence that the pathology itself causes the obstruction from within. The example of myomata, fibromata, and polyps of the tubal wall causing narrowing, places such entities as obstruction from without--- but in most cases reported it is found that the new growth itself has not been large enough to mechanically cause the block. What then is the answer in cases of this nature? DeLee (11) states that there is an edema of the mucosa of the tube following such growths in the wall. The same response is found in other mucous lined tracts and is certainly a possibility in these cases. He further states that spasms of the tubal musculature (similar to spasm of the musculature of the bronchi in asthma), muscle insufficiency, and anti-peristalsis are further possible causative factors.

Infantile tubes with lack of cilia may be a factor which causes ecchyesis (11).

3. Anomalies of the tubes.

In this category we find seceral opinions as expressed by Schumann (1) who has sited Webster, Hirst, and Knipe. Webster believed that the sole cause of ecchyesis was that the ovum imbeds in mullerian tissue. The fact that ovarian pregnancies seem to occur caused Webster to modify his opinion and say that mullerian rests must occur in the ovary as well as in the tubes in order to give rise to such a phenomenon.

Again, Schumann (1) sites a theory advanced by Huffman in which Huffman believes that extrauterine pregnancies occur in decidual tissue which is misplaced. The evidences of misplaced uterine decidua can not be denied, but most authors are convinced that this alone is not the cause of all of these cases. DeLee (11) believes that misplaced decidual tissue is one of many factors involved. "Huffman (1) goes further to explain ectopic gestation in those cases in which decidual reaction can not be found near the imbedded site, by saying that malformations of the tubes, accessory ostia, congenital diverticulae, etc. will almost always be found if searched for with enough diligence." Williams (5) has this to say, "the presence of true tubal diverticulae seems to be one of the rarest of tubal malformations, whereas false, pseudodiverticulae are found in a large per cent of tubes as a result of inflammatory affections." Newell (6) sites

Hall (journal not available) as saying, "Cosgrove has another unique explanation. He assumes the presence of an extra-uterine endometrial transplant in which the fertilized ovum comes to rest and then develops in this ectopic endometrial tissue."

4. External migration of the ovum.

Cases reported in which one tube and the opposite ovary have been removed and a subsequent tubal pregnancy in the remaining tube have led some writers to believe that when the ovum has a long distance to travel it loses its vitality, grows larger, or is an abnormal ovum and does not pass through the tube, or becomes impregnanted and develops in the aberrant site. This theory is upheld by DeLee et al (11). It can neither be denied nor admitted in a paper of this type.

Mueller (1) reports that associated hormonal deficiencies may be associated with external migration of the ovum even when both tubes are patent. Such may be the case for it is this writer's opinion that there must be a definite chemical attraction of the tube for the ovum, or ovum to tube, to cause the ova's entry into that tube in normal individuals. It is hard to explain the entry of the ovum into the tube merely by the mechanical sweep of the fimbria. It would be easily possible by any exertion at the time of ovulation for the ovum to escape the tube. Therefore, I feel that the hormonal theory holds great promise

in establishing one of the causes of ectopic gestation. Mueller does not stress this theory but maintains that the hormonal reaction is by the musculature of the tube and may cause a lack of peristalsis of the tube or a general disturbance of the musculature.

A unique theory advanced by Mahfouz (9) is that, "a very rare cause of ectopic fetation is post-operative separation of the edges of the uterine wound of a previous caeserian section. Four cases of this kind, in which primary abdominal pregnancy occurred, are reported by E.L. King. "

The causes of ovarian pregnancy are even more speculative than are those for tubal pregnancy and as many theories as there are authors exist.

In a recent article by two Russian authors (Osiakana-Rajdesivenskaia(12), an entirely different classification is given as to the etiology of ectopic gestation.

"1. a. A peculiar faculty of the female reproductive cell to impart to the ovum the capacity for premature implantation, i.e. before it reaches the uterus.

b. Disturbed transportation of the ovum.

c. Mechanical obstacles encountered on the journey of the ovum which either handicap or make impossible its further progress.

2. All three factors are closely connected with one another, and, therefore their distinction

from one another can be only approximate. However, the outstanding cause is apparently the second factor, i.e. disturbed transportation of the ovum for in all probability it may be the independent cause of tubal pregnancy, while the first and third factors, play a merely relative part and must be accompanied by disturbed transportation, however slight, to cause tubal pregnancy.

3. The motor capacity of the tube depends to a great extent on the effect of the vegetative nervous system which may in turn be influenced by various emotions, i.e. fear of pregnancy, abortion, and the administration of contraceptive measures.

4. We believe that factor a is operative in 10% of cases, b in 16%, and c in 76%.

5. Among mechanical causes, defective development of the tube of post-embryonic nature seems to be of prevailing importance.

6. Improvement of the living conditions, less frequent occurrence of infectious diseases, and better working conditions for growing girls will reduce the per cent of extra-uterine pregnancies."

ANATOMY AND PATHOLOGY

The Fallopian tube is made up of three coats; an inner mucous, an outer serous, and two layers between of muscular tissue, one of which the fibers are arranged in longitudinal bundles, externally, and one with its fibers disposed in a circular direction, encircling the lumen of the tube, internally. The lining mucous membrane is covered with a single layer of epithelium, in the form of high, columnar, ciliated cells, which rest upon the thin basement membrane. There is no submucosa, the epithelium being separated from the underlying musculature by a layer of connective tissue of varying thickness, this arrangement corresponding with that of the uterus. The mucosa is thrown into folds, simple at the uterine end of the tube, and becoming more complex as the fimbriated end is approached.

The muscular elements of the tube possess peristaltic powers which aid in the transportation of the ovum from the ovary to the uterus. The cilia of the lining epithelium likewise are definite aids in the transportation of the ovum as they have been shown by Pinner to beat toward the uterus (1).

The large subdivisions of the tube, as seen grossly, are known as the ampullary portion, an enlargement lying near the ovary; the isthmial portion which makes up the bulk of the tube; and the interstitial

portion, which passes through the substance of the uterus some short distance.

The relative occurence of pregnancy in the portions of the tube mentioned, as well as the occurence outside these structures, can be seen by the chart compiled by Mahfouz (9). Of a series of 120 cases he found the following locations:

Ampullary and Isthmial	96
Interstitial	4
Tubo-ovarian	3
Tubo-ligamentary	6
Tubo-abdominal	4
Ovarian	1
Primary abdominal	1
In a rudimentary uterine horn	5
	120

Murray (42) in a series of 146 cases found approximately the same per centage occurence in these structures as did Mahfouz.

The mode of implantation of the fetus in the tube may vary. Columnar imbedding, which is exceedingly rare, occurs when the ovum attaches itself to one of the tree-like folds of the tubal mucosa, later becoming attached to others of these folds, but no place in contact with the tube wall itself. The ovum obtains its nourishment from the mucosa but later erodes its way into the tube wall. Intercolumnar implantation occurs when the ovum comes to lie in the crypts between the folds of the tube and erodes its

way into the tubal wall. It is believed that when the ovum establishes contact with the blood vessels of the tube wall that chorionic elements invade these blood vessels and obtain nourishment for the ovum. After the ovum grows so large an rupture occurs it is believed that most of the hemorrhage comes from these eroded vessels.

"Whether a true decidua is formed following implantation is a moot question. Schenck and Frankel in advancing their endo metrial etiologic theory of ectopic pregnancy, felt that usually endometrial tissue was present in the tube which by hormonal stimulation became decidual tissue. Conversely Falk stated that the stroma of the tube usually does not undergo decidual changes to resist the digestive action of the trophoblast of the ovum, and Litzenberg contended that there is no true decidua in the tube, that there is an ovum bed but no decidua basalis and very few decidual cells." It appears that this question is of purely academic interest as after implantation has occurred, treatment is necessary. (29-42).

"The tubal and the uterine placentae are identical in formation, with the difference that, as development proceeds, the thin tube wall, lacking the true decidua serotina, is easily invaded by the trophoblast and syncytial cells, since there is no active connective tissue reaction set up by the tube with the presence of fetal cells. The villi rapidly

penetrate the tube wall and are found just beneath the serous coat, which is in turn invaded, with resulting rupture. The tubal placenta also suffers from a lack of nutrition, the false sinuses formed by the penetration of tubal vessels by the trophoblast being not comparable to the rich blood supply developed in the uterine wall. Microscopically the tubal and uterine placentae are identical in all respects (1).

The results of ectopic pregnancy are: (25).

I. Ovarian pregnancy.

Sac develops in substance of ovary, usually with early rupture.

II. Tubal gestation.

In the (1) isthmus, (2) ampulla, (3) accessory Fallopian tubes (rare), in the fimbria (4) (rare).

A. At times it progresses in the Fallopina tube to advanced stages of pregnancy without rupture, but this is very rare.

B. Intraperitoneal rupture, most common results.

1. Death from profuse bleeding.

2. Hematocoele which may undergo

a. Absorption

b. Suppuration

3. Fetus may develop in peritoneal cavity, placenta remaining in tube (secondary abdominal pregnancy). May go to full term, or sac may rupture at any time. Fetus may undergo secondary changes as

a. Mummification

b. Adiopocere

c. Calcification

d. Suppuration.

C. Tubal abortion

Expulsion through abdominal ostium may result before occlusion occurs, i.e. before eight weeks, may persist as a tubal mole and is of two types

1. Complete expulsion known as hematocoele.

2. Incomplete with recurrent hemorrhage intraperitoneally, often fatal.

D. Hematosalpinx

Death of embryo with rupture; tube filled with blood clot may become infected--pyosalpinx.

E. Rupture into broad ligament.

1. May continue to develop till term as an intraligamentous pregnancy.

2. May develop for a time and then 'secondary rupture' into peritoneum occurs.

3. May form a hematoma, following death of fetus, and results in

a. Absorption.

b. Suppuration.

4. Suppuration of gestation sac. Rupture may occur into

a. Bowel.

b. Bladder.

c. Vagina.

d. Abdominal wall.

III. Interstitial pregnancy.

Develops in portion of tube in uterine wall. Sac ruptures fourth month of pregnancy into

1. Peritoneum

May be fatal from hemorrhage.

2. Uterine cavity (rare).

IV. Cornual pregnancy.

This is rare and ends in intra-peritoneal rupture after third month.

V. Primary abdominal pregnancy.

This is very rare and is questionable.

In going over the literature of this subject it is found that there is a notorious omission as to the pathology by most authors. This concerns the fact that tubal pregnancies as well as all other pregnancies, may give rise to the same pathological picture in the patient as normal pregnancies. Most authors consider ectopic gestation as an entity. It is not. The changes that may occur in a normal pregnancy may occur in an ectopic. Some of these are breast changes, changes in the external genitalia, and even changes resmbling those of toxemias.

The fate of the fetus depends largely upon its ability to get nourishment and have an adequate space in which to grow. In the great majority of cases of extra-uterine gestation the embryo is destroyed during the early weeks of development. Most of these early embryos are destroyed by hemorrhage which is

produced for their nourishment near the site of implantation. If the dam built up by the trophoblast is sufficient to check the flood in part, enough villi will remain to nourish the ovum. When the tube ruptures into the broad ligament the space for the chorion becomes sufficiently large for new villi to grow and attach themselves. Rupture, when it occurs on the free side of the tube, throws the embryo into the peritoneal cavity and usually terminates its career. Whenever the degree of alteration of the tube wall is pronounced and accompanied by marked infection, the ovum does not implant well, and consequently the ovum does not develop normally, but becomes atrophied and degenerated. The more sefere the inflammatory process the more pronounced is the deformity of the embryo.

If a fetus should go to term there are two main factors which hinder its development. These are the lack of proper nourishment and the lack of suitable space in which to grow. It is for these reasons that many of those cases reported where the gestation has gone to term (usually secondary abdominal), that the fetus has all sorts of monstrous deformities.

If extra-uterine pregnancy is not diagnosed, the patient does not see a physician, or the gestation is past term, a false labor may ensue. At this time there are short, false labor pains which gradually subside and the woman may not have thought herself pregnant. In these cases after the false labor

the placenta degenerates and the fetus dies. Terminal changes take place in the body of the child. These changes are suppuration, skeletonization, lithopedian, mummification, adipocere, or saponification. There is real danger to the life of the mother from such a long retained fetus although many of them are carried for years. Infections, perforations of a viscus with infection, pointing, or chronic abscesses are the most frequent pathological features encountered in cases of this type. In all cases of retained fetus, after fetal death, the fetus acts as a foreign body and should be treated as such (1).

SIGNS AND SYMPTOMS

In presenting a discussion of the signs and symptoms of extra-uterine gestation one is faced with the task of great condensation and elimination of material. This discussion will not include laboratory signs. Such a discussion will be found in the section on DIAGNOSIS.

A. Symptoms.

1. Menses.

In the experience of those authors who have chosen to carefully study this condition it has been found that there is always some sort of menstrual disorder, either recognizable or unrecognizable by the patient. Where the patient had previously been regular in her periods the disturbance may vary from some slight irregularity to a gross amenorrhea.

Sessums (13) reports that out of 60 cases, 56 gave a definite history of some menstrual disorder. 40 of his cases had an amennorrhea, while 6 complained of metrorrhagia. 4 cases showed no disturbance whatsoever in the menses. Hennessy (14) gives approximately the same percentages for the presence of these symptoms, but does not agree that there no disturbance in the cycle.

Joss (15) states that in all the cases he has seen there has been some sort of menstrual disturbance. This may vary from slight delay to a prolonged dribbling and spotting. "Delay, prolongation of the normal period, or alteration of the character of flow is

always present." He goes on to say,"---a prolonged dribbling where the patient previously had been regular is practically always pathognomonic."

White (16), an Australian, believes that the patient usually misses about one period. Following the missed period by about two to three weeks other symptoms are ushered in. However, he believes that the missed period may be initiated at the time that the other symptoms appear, and that this period then is much more profuse than any of the previous regular periods. After the onset of the various other symptoms, frank hemorrhage from the uterus may take place. This is not an acute hemorrhage but as White says is a, "chronic dribble acquiring the proportions of severe blood loss after a few days." This flow is more likely to be a dark brown, and resembles coffee grounds. "This flow remains until the fetus is removed or is absorbed."

"When a woman of the childbearing age has any sort of menstrual disturbance with accompanying lower abdominal pain, the attendant must always suspicion extra-uterine pregnancy (17)." Such conditions co-existing are pathognomonic of ecchyesis (18-19).

In going over 25 cases histories in the University files I found that each patient suffered some prolongation between her previous normal period and the period which could be considered pathological. This finding would substantiate the

statement by Ware and Winn (24), "if careful inquiry will be made it will reveal amenorrhea, that is, a cycle of more than 28 days before vaginal bleeding".

Baens (20) states that there is always some sort of menstrual disturbance noted by the patient but that unless very careful questioning is made this bleeding from the vagina will be interpreted to the physician as a normal menstrual period. Baens does not uphold the relative amenorrhea theory. There is easily liable to be confusion arising on this point as many times patients are over zealous in their attempts to aid the attendant and many times they just don't pssess the mentality to remember exact dates. Unless the menstrual disturbance is gross, very few patients will notice any irregularity. Watkins (21) goes along with Baens in believing that most patients will show some sort of vaginal bleeding shortly after the expected date of menstruation, but in that series three cases of amenorrhea are reported. Jonas (23) agress that bleeding is not always present, in which cases there may be marked confusion as to diagnosis.

Tractenberg (22) gives a description of the usual course of events. "---in tubal pregnancy there appears some menstrual disturbance. The menses stop and the patient believes herself pregnant. About six weeks later (after the last regular period) dribbling of dark brown blood appears. It may continue as such,

or as in several cases of mine spotting may occur only on one or two days of each week. Some menses of these patients come at the normal time but continue as dribbling and the flow becomes dark brown in character with many fibers noted in it."

2. Pain.

Pain in extra-uterine gestation is of a very peculiar nature. It is only localized in the pelvis at the outset and from there may be referred to any place within the abdominal cavity, back, shoulders, or legs. The reference of the pain is due to peritoneal irritation. The peritoneum even before rupture may grossly be irritated by the expanding tube which does not offer much protection. Early the pain is localized, after rupture the most bizarre picture of pain may be present. When rupture occurs (or in tubal abortions) blood is extruded into the peritoneal cavity. Fresh blood is an irritant to the peritoneum and gives rise to pain by stimulating those pain receptors located in the peritoneum. It is seen that at any point at which the peritoneum is stimulated by an irritant pain arises. This accounts for the diffuse, referred pain.

Baens (20) in a series of 174 cases found that the pain was referred to the following areas:

Area to which referred	Cases
Epigastrium	16
General abdominal	6
Chest	2

Area to which referred	Cases
Loins	1
Shoulders	6
Back	3
Right subcostal margin	1
Left subcostal margin	1
Flanks	1
Anus	9
Perineum	5
Thighs	2

While only 56 cases of pain out of a total of 174 cases it seems unreasonable that the remainder were without pain. Nevertheless, this report shows the wide variance with which pain may manifest itself.

The type of pain present also varies. In early cases in which rupture has not taken place the pain may be "cilicky" in nature or may be only a vague sensation of something pulling or weighting down the individual (23-16). Several authors have stated that pain may be entirely absent (21-24). Such reports are denied by Curran and Goodale (19) who state that if there is one constant symptom representing this condition--it is pain.

Usually following the delayed or irregular menstrual period by a few days to about two to three weeks, a severe, knife-like pain is noted in the lower abdomen. This pain may quickly become diffuse or referred, but by careful questioning it can be determined

to have had a point of origin such as the iliac crest, just above the symphysis, etc. This pain may cause severe distress, the patient being unable to move, stand upright, or lie still in bed. It has been described as unbearable torture. The pain usually reaches its height in about one-half hour and gradually subsides. It usually leaves a residual soreness in the area of its beginning for a day or two. The sharp, knife-like pain may return or may be entirely absent (13-15-22-23). The original site of the pain may or may not be over the affected side. Sixty-three percent of Ware and Winn's (24) cases showed the pain to be over the affected side. Varying percentages are reported by other authors. At the time of the severe pain the patient may become dizzy, weak, vomit, or just nauseated. She may continue in this weakened condition or recover fully (11). Shock and death may ensue.

Rectal pain with or without defecation may persist after the original attack. Urinary pain may also be present and may be associated with burning on urination (19). These are not constant symptoms.

3. Other symptoms.

Abdominal tenderness even before rupture may be present. This is often very distressing to the patient and many times is the exciting cause of the visit to the physician.

Vaginal tenderness has been described. In one case reported tenderness of the vagina on coitus was the only presenting symptom. Another complained

only of a vaginal mass noticed while taking a douche (23).

Vomiting and fainting are very distressing and may be the cause of the patient staying away from the physician by making her think that she is normally pregnant. These symptoms may mislead the attendant for when they are associated with amenorrhea a normal pregnancy is always suspicioned. It must be remembered that extra-uterine pregnancy is truly a pregnancy and that all of the early symptoms of a normal pregnancy may be present. The physician will make fewer diagnostic errors as concerns this condition if he will bear in mind that ectopics are possible.

As mentioned, any degree of shock may be present. Shock may be all out of proportion to the apparent amount of blood loss or may manifest itself early as merely a weakness (13).

Extreme thirst has been reported as the only presenting symptom (25). Anuria, frequency, dysuria, and burning on urination were present in 28% of Livendahl's cases (26). Icterus with dark stained urine may be a symptom.

Many patients complain only of chills. Of course this is one of the many manifestations of shock and should be carefully studied. Some patients complain of difficult breathing. Such is probably due to diaphragmatic peritoneal irritation which causes a splinting of the diaphragm (19).

B. Signs.

In all of medicine whenever a pathologic condition has been known to exist, signs for the betrayal of the presence of that condition have been sought. In the case of tubal gestation many signs have been found, but as with symptoms, there is no one sign that is pathognomonic.

1. Cullen's or Hellendahl's sign.

Shortly after the first World War a man by the name of Cullen noted that in cases of ectopic pregnancy there was prone to develop a discoloration about the umbilicus. The discoloration was blue, blue-black, or jet black (27). This is known as the "blue belly button" sign by the laity. It is not constant and according to Livendahl (26) it was present in only 6 of 1410 cases reported in the literature.

Since Cullen described this sign there has been much comment. It has been found by Brady (27) to be present in many cases that have been previously operated, but not at the umbilicus. It appeared in the old scar which gives rise to the opinion that it may occur at any point where the abdominal wall is thin, or where the pigment cells have been destroyed. Other locations for this sign have been in herniae, fistulae, etc. This sign is present not only in ectopic gestation but also in cases where there is intra-abdominal bleeding from other sources. Cullen's sign may be present before rupture and massive hemorrhage. Brady (27) states that if this sign is present before

rupture it is then due to extravasations of blood through the open end of the tube.

Associated with this sign there has been described a contraction of the pupil on the side of the hemorrhage or location of the pregnancy (28).

2. Shifting dullness---fluid abdomen.

Jonas (23) reports that in many cases following rupture and extravasations of blood, an area of shifting dullness may be found in the abdomen on physical examination.

3. Shifting pain.

Lifvendahl (26) reports the discovery of a new sign dependent upon the shifting of pain from one area to another. The patient may be lying in bed or sitting in a chair and notice that on shifting her position the pain will transfer itself to another area. Such shifting of the pain takes about ten to fifteen minutes. This sign is not constant and is present only when there is free, unclotted blood in the abdomen. The shifting of the pain is due to the irritation of the peritoneum in another area by the free blood.

4. Temperature.

There is only slight elevation of the temperature in these cases, even after rupture. The highest temperature recorded is 103. The average is 99 (14). In cases where infection is present the temperature may be higher.

5. Pulse.

The pulse rate is directly proportional to the amount of shock present and to the amount of blood loss. It varies from 50 to 160 per minute and averages 94 per minute in cases reported.

6. Respirations.

The respirations may be rather rapid due to a large amount of blood loss, may be normal, or may be markedly depressed dependent upon the amount of shock.

7. The blood. (Please see section on DIAGNOSIS)

8. Abdominal distension.

Distension may be present to a marked degree or may not be present at all. When present it usually indicates a massive intra-abdominal blood and fluid loss. However, it may be present in cases of paralytic ileus due to shock.

9. Vaginal examination.

On vaginal examination there is found one almost constant sign. That is pain when the cervix is moved (13-14-16-19-20-21-22-23). Most of these authors also report that there is a perceptible softening of the cervix. Enlargement of the uterus is usual. At the time of full term in ectopic pregnancy (usually secondary abdominal) the uterus is about the size of a three months normal pregnancy. It is proportionately smaller in earlier months. Haeger's sign and internal ballottment are absent (16). Chadwick's sign is present in

20% of cases (21). There may be a sense of fullness in the cul-de-sac by the examining finger. A bulging of this structure may be noted. A pelvic mass in either quadrant is present in 80% of cases (13). This mass may displace the uterus, lie beside it, or may lie above it. The cervix may be displaced and if so is usually pulled upward and backward.

10. Jaundice.

Icterus may be present in those cases with old ruptures in which the blood pigments have had time to resorb. The jaundice may also be due to liver irritation or to spasm of the ductus choledochus or common duct (11).

11. Discharge of decidua.

As shown in the section on PATHOLOGY, the uterus builds up a decidua wherever a pregnancy is located in the body. Whenever that pregnancy is interrupted, or the fetus dies, and there is no more stimulation, the uterine decidua is cast off. It may be cast off piece-meal or in one mass, called a decidual cast. Microscopic examination will readily reveal the type tissue present and the absence of chorionic tissue. This is a tremendous aid in ruling out incomplete abortion (16).

12. Breast changes.

As has been noted, ectopic pregnancy early resembles a normal pregnancy. Thus, the breasts may become tender, sore, enlarged, darkened about the areolae, and even engorged (14).

13. Rectal hemorrhage.

In a case report, J.B.Dawson (18), states that the patient had profuse rectal hemorrhage due to a secondary implantation of the placenta on the transverse colon. Tenesmus was severe. This sign has been acknowledged by other authors but was found present not only in cases with secondary implantation on the colon, but in cases where peritoneal irritation near the colon was severe and defecation furthered the process.

DIAGNOSIS

The section on diagnosis will include those things which may be done by the physician to aid him in accurately determining the exact pathological process present in the patient.

1. History.

In any case presenting pelvic complaints a careful, concise, accurate history should be obtained. A thorough history of the menses, their occurrence, duration, character, associated cramps, regularity, and above all, any change noted by the patient, is absolutely necessary. History of pain, previous ecchyesis, operations upon the pelvis or abdomen, period of relative sterility, relative length of the sex life, primipara or multipara, should accurately be obtained. History of previous infections, or possibilities thereof, is very important. An exact chronology of the sequence of events, onset, type pain, character, what followed what until the present time, is the only way in which the history should be elicited. Many times by a careful history alone a presumptive diagnosis can be made which is correct more times than incorrect as concerns this condition.

2. By Physical examination.

Anytime a patient is seen by a doctor that patient deserves the attention of the physician and should be given a thorough physical examination.

3. By laboratory procedures.

a. For temperature, pulse, and respirations as seen in this condition, please refer to section on SIGNS AND SYMPTOMS.

b. The blood pressure.

As the pulse varies, a direct proportional variation in the blood pressure will be found. It may be very low both systolically and diastolically or may be greatly elevated. It may be normal. Those patients in shock will be found to have a very low, almost indeterminable blood pressure, while those seen before rupture will have nearly a normal reading. In the literature there are found those case reports in which a markedly elevated pressure is found which resembles the pressure of a toxemia. These findings are usually in those cases with a late unruptured tubal pregnancy or a secondary abdominal pregnancy in which real toxemia is present.

c. The white blood count.

The white blood count may be found well within normal limits, elevated, or depressed. The majority of authors report that the count runs from 10,000 to 20,000 and is in a direct proportion to the amount of peritoneal irritation caused by the escape of blood. It gradually subsides after a hemorrhage, but may again rise after a subsequent hemorrhage. The highest reported count was 45,000 but in this cases there was an intercurrent infection in the pelvic hematocele.

Cases in which a leucopenia exists are rare but such are found occasionally. The leucopenia is explained on the basis of enormous quantities of blood loss with little response of the bone marrow to produce new cells.

d. The red blood count.

The red blood count will vary in a direct proportion to the amount of hemorrhage. It has been reported as low as 1,500,000 per cubic millimeter. It generally is found about normal in those cases of unruptured ecchyesis, but may be found markedly lowered in those cases of hemorrhage. "Every gynecologic diagnosis with a red blood count below 3,500,000 should not exclude extra-uterine gestation (30).

e. The hemoglobin.

The hemoglobin varies ina direct proportion with the red blood count. A hemoglobin as low as 6 grams per 100 cc of blood has been reported (30).

f. The sedimentation time.

There is much confusion in the literature as to just exactly what can be expected of the sedimentation time. One author reports that the rate is always increased (31). The majority of authors are agreed, however, that the rate is directly proportional to the amount of peritoneal irritation and that the same factors that influence the elevation of the white blood count are effective in increasing the sedimentation rate.

g. The differential blood count.

This count, as would be expected, varies as the white blood count. In those cases showing an elevated white blood count there is a shift to the left in the differential count. In the cases of long standing, chronic hemorrhage, immature cells may be found, however, this should not cause alarm in itself as it indicates a good bone marrow response in the patient.

4. Special diagnostic aids.

a. The Ascheim-Zondek test (32).

In 1928 Siddall injected the serum of pregnant women into immature female mice and produced a remarkable growth of the genital organs. Zondek and Ascheim published a test based on the fact that a peculiar hormone is excreted in the urine of these patients. Their experiments seem to prove that the anterior lobe of the pituitary gland produces two hormones. One stimulates the ovarian follicle to hasty ripening, the other hurries the lutienization of the same. This double hormone is found in the serum, pregnancy colostrum, saliva, decidua, and urine of pregnant females. There is considerable arguement as to this hormone's origin. Suffice it to say here it is found in many organs all of which are intimately associated with pregnancy and the propagation of the species. In a liter of normal urine there are 50 to 100 rat units of these hormones, but in pregnancy there are 12,000 rat units or more.

"The urine of pregnant women therefore contains

a new element, when injected into immature mice or rats produces such activity of development of the genital organs that it is striking to the naked eye--- rarely needing a microscope (11). The technique of this test is rather simple and will not be recitied in detail here. For further information any standard text on obstetrics will carry the details.

It is seen that this test is dependent upon the secretion of a new substance by the glands and organs of pregnant women. In cases where there is a doubtful diagnosis, as in extra-uterine gestation before rupture, and also as a differential diagnostic test, this and other hormonal tests are very useful and should be employed. However, a word of caution is necessary--- these hormonal substances may not be present if the fetus is dead. Neither do these tests produce a 100% accuracy. The accuracy varies from 95% to 98% if found positive. Negative tests do not rule out pregnancy. Teratomata, chorionic epitheliomata, hypophyseal tumors, etc. may give a positive result. Corroborative evidence must always be sought before giving a final opinion (11).

b. The Friedman and similar tests.

Friedman, Stricker and others have used various modifications of the original Ascheim-Zondek test and have claimed better results. Friedman used rabbits and injected urine into the marginal ear vein. He then examined the internal genitals, although changes also

occur in the external genitals. Hyperemia, hemorrhage, and general maturing of the impregnated rabbit are considered positive. Adult, young unimpregnated rabbits are used. The rabbit does not ovulate until coitus. Thus, when an animal is known not to have been near a male is used and upon examination changes resembling those after coitus are found, the test is considered positive. The same precautions and judgements must be used in this test as in the rat or mice tests (11). The Mayo Clinic has found this test to surpass all others for accuracy (34).

De Lee (11) has used the male mouse and rat for the injections and has found that the external genitals of these animals undergo the secondary sexual changes when impregnated with the urine of the pregnant female. This is another modification of the original test by Ascheim and Zondek.

c. New test. (The frog test).

A new pregnancy test has been devised. It is similar in principle to the older tests. It seems so much simpler, more economical, and quicker, that it will be recited in full including the technique of the test.

Weisman, Hoenig, and Coates are the authors who report their results with this test (33).

This test was first suggested in 1934 using the South African clawed frog. Three thousand tests abroad report 98% to 100% accuracy with this frog. The time

factor is greatly lessened in this test for pregnancy, i.e. four to eighteen hours. Results reported cover fifty-three cases.

Xenopus laevis carries eggs during the whole year and only extrudes them on mating or on injection of hormones peculiar to pregnancy. The animals are kept free from males and any extrusion of ova following injections of suspected urine containing gonadotropic hormones is considered a positive test.

Test	Xenopus laevis	Friedman
18	18 negative	18 negative
33	33 negative	33 negative
33	33 positive	33 positive
1	1 positive	negative
1	1 positive	negative

In the first disagreement of these tests the frog indicated pregnancy and the rabbit didn't. However, owing to the history and clinical findings the patient was operated with a preoperative diagnosis of ectopic pregnancy. An unruptured tubal pregnancy was found.

In the second disagreement the frog was positive. One week later the tests in both animals were repeated and were both positive, indicating the frog test may be more sensitive than the rabbit.

The advantages of the frog test over the rabbit and mice tests are shown in the following chart.

	Frog	Mice	Rabbit
rapidity	4-18 hrs	96 hrs	36-48 hrs
simplicity	no operation	requires operation	requires operation
economy	16¢ per frog	5 mice-$1	1 rabbit-$1.50
maintenance	simple	feeding and cleaning problem	space occupying
technique	single injection	40 injections	1-2 injections
ease of injection	subcutaneous	multiple injections	intravenous
practicability	can be used over & over	animals killed	rabbit usually killed
special precaution	none	age and weight	isolation
end reaction	simple observation of eggs in water	search for ovaries in five animals	search for ovaries

Technique of test:

The frogs are kept ina simple tank. They are fed on beef heart, garden worms, or liver twice a week. The tanks are kept at room temperature. If they develop an odor the water is changed to that of the same temperature with fresh water. The test tank is separate. It is equipped with a wire mesh about one-half inch from the bottom to prevent the frog from devouring its own eggs. Before each test the wire mesh is burned with a bunsen burner as some of the eggs from a previous test may be present and foil the test.

Concentration of Urine:

Whole urine may be used but on concentration a more rapid extrusion of eggs is possible. Use 80 cc

of urine acidified until acid with glacial acetic acid. 160 cc of acetone are used and added causing a precipitation of hormone and protiens from the urine. The contents are mixed thoroughly. Let stand fifteen minutes. Centrifuge. The precipitate is washed two times with ether. Allow the precipitate to dry. Two cc of distilled water are added and then mixed and poured into a centrifuge tube. This brings down the protien while the hormone is soluble in water. Adjust the Ph by nitrazene paper with sulfosalicylic acid to 5.5. 1 cc of the final solution is equivalent to 40 cc of whole urine. 1 cc is injected while the remaining solution is saved in case of a re-check.

Method of Injection:

Inject into the dorsal lymph sac of the frog taking great care to miss the lung.

Reading the Test:

Place the animal alone in the test tank and observe. Extrusion of eggs may be within four hours. Read the test at eight and again at twelve hours. It is usually complete at this time. If no eggs are found at the end of eighteen hours, the test is considered negative and the frog is placed into the resting tank and used again in three to four weeks.

Other Hormone Reactions:

Progesterone, testosterone, anterior pituitary like substances when injected in large doses may cause extrusion of eggs. These substances are not present in

in quantity in any type pregnancy to cause extrusion of the eggs.

d. Falls (35) reports another test which is also simple and quick. It consists of skin reactions and variations found in pregnant and non-pregnant women.

After puberty it appears that all male and female humans are sensitive to human colostrum. After a woman has become pregnant there is a productions of colostrum in the breasts. This production of colostrum appears to immunize these pregnant women against colostrum when injected subcutaneously. Therefore, when a small amount of colostrum is injected subcutaneously in a pregnant woman, no sensitized wheal develops. If the woman is not pregnant a wheal several centimeters in diameter will develop and will last with an erythematous border for about three to four hours. The wheal develops in twenty to thirty minutes. This test is found correct in about 80% of all pregnancies and is found correct in about 85% of those cases of extrauterine gestation. It would seem that such a test is invaluable although a negative test (the presence of a wheal) could not rule out a pregnancy. Corroborative evidence is needed here just as it is needed in the other hormonal tests.

e. Other tests.

Various other tests have been reported to tell the presence of free blood in the abdomen as associated with ecchyesis. The Van den Bergh test may be pos-

itive due to the absorption of old blood pigments from the pelvic or abdominal hematocoele. A positive pyramidon test may be found. Hyperbilirubenuria and hyperbilirubenemia are usually found if the Van den Bergh is positive.

5. Colpocentesis.

This test depends largely upon rupture and the presence of free blood in the abdomen to be of significance.

Falls (35) gives the following rules to govern colpocentesis.

a. There must be a mass in the cul-de-sac sufficiently definite to indicate the direction of the diagnostic puncture.

b. Use a large aspiration needle so that small clots may be extracted.

c. Surgically prepare the vagina.

d. Needle only to the hematocoele and if and when old blood is encountered---stop.

e. When old blood is hit it gives enough evidence for laporotomy.

Miller (30) agrees whole-heartedly with these suggestions and states that they should be followed very closely.

There is another group who believe that this procedure holds too many dangers and should not be tried. Grier (36) is a chief disbeliever. Nixon (37) believes that this procedure should not be attempted unless there

is pulsation in the fornices and that if pulsation is present the test with its added dangers of infection is not needed.

6. Curetage.

In cases of pregnancy, no matter where that pregnancy is located, there are decidua like changes which occur within the uterus. These changes are of the true maternal decidual nature. Therefore, a group of workers contend that curetage with findings of decidua and absence of fetal chorionic elements is evidence that there is a pregnancy but that the pregnancy is outside the uterine cavity. This procedure is also considered an excellent differential diagnostic test. Goldblatt and Schwartz (38) have published an article concerning the stage of the endometrium in relation to the Friedman test. Their findings would indicate that the Friedman test is all right but that it can't be relied upon as can curetage. If the fetus dies the Friedman becomes negative within ten days while the decidual like changes in the uterus may continue until the fetus is extricated. This is not always definite as in many cases the decidual like substance is expelled as a cast and subsequently the findings on curetage may be those of a non-pregnant woman. However, these men contend that the decidual like changes are more accurate in diagnosis than are the laboratory procedures.

TeLinde and Henricksen (39) have found and reported

a cases in which a decidual like change was present in the uterus without the presence of any form of pregnancy.

Lowry (40) states that either the posterior colpotomy or the diagnostic curetage are very dangerous procedures and are to dangerous to be carried out. He states that the possibilities of infection offset the possible values of these tests, and that in cases where there is as much evidence present as these procedures necessitate before being performed, the diagnosis should be obvious without further insult to the already very ill patient.

7. X-ray.

Snow (41) and his cohorts in New York City report three cases in which the diagnosis of extra uterine pregnancy was ascertained through the use of soft tissue roentgenological studies. They studied the shadows cast by the uterus, placenta, fetal parts, etc., and correlated these shadows with those of normal pregnancies. They used dyes in the bladder and studied the shadows cast by the uterus upon the bladder, also the indention of the enlarged uterus into the bladder. In this manner they could determine the size of the uterus and correlate this with the duration of the pregnancy. This method is, of course, only useful in those cases of late ecchyesis. It was found useful in those late cases where a differential diagnosis was needed. This method is excellent in determining late abdominal pregnancies.

DIFFERENTIAL DIAGNOSIS

"No pelvic condition gives rise to more diagnostic errors than extra-uterine pregnancy." (11)

"The most typical thing about an extra-uterine pregnancy is that it atypical." (45).

In dealing with a condition in which most authorities readily admit the diagnosis is most difficult, and often impossible, it can be seen that many errors will be committed. It is the purpose of this section of the paper to relate some of those errors and to incorporate methods by which they may be overcome.

In reviewing the literature it was found that authors are reluctant to report diagnostic errors concerning this subject. However, two very excellent reports have been given by a group in New Orleans and a group in Chicago.

Graffagnino, Seylor and Bannerman (44) in New Orleans report the admission diagnoses on patients later found to be suffering from ecchyesis in the New Orleans Charity Hospital of Louisianna.

Diagnosis	Cases
Ectopic pregnancy	276
Abortion	26
Chronic pelvic cellulitis	15
Bilateral salpingitis	11
Acute pelvic cellulitis	13
Cystic ovary	16
Fibroids	22

Diagnosis	Cases
Pelvic abscess	6
Salpingo-oophoritis	12
Tubo-ovarian abscess	16
Acute appendicitis	11
Chronic salpingitis	9
Pyosalpinx	5
Subacute appendicitis	4
Dermoid cyst	1
Left ovarian cyst	1
Acute indigestion	2
Endometritis	2
Cholelithiasis	1
Right salpingitis	1
Peritonitis	1
Typhoid fever	1
Intestinal obstruction	1
Ruptured uterus	1
Prolapsed uterus	1
Puerperal sepsis	1
Retroverted uterus	1

Miller (30) in Chicago reports approximately the same variations as to diagnosis and the percentages for which each was given. It can be seen from theser reports that errors are not individual but are rather constant for the whole profession.

Some of the more common diagnostic errors listed above will be discussed and suggestions made

to avoid these errors.

1. Abortion.

In abortion the bleeding is usually more profuse, with clots; the pain is caused by intermittent cramps located over the uterus and gradually in creasing. Fetal parts or villi in the vaginal discharge render the diagnosis of abortion certain.

A diagnosis of ectopic pregnancy is quite certain when there is fever, leukocytosis, great pain on moving the cervix and an exquisitely tender, pulsating mass at one side of the uterus.

2. Salpingitis.

A history of recent gonorrheal infection, positive smears, purulent discharge, gradual onset, high fever, leukocytosis, no enlargement or softening of the uterus, a hard cervix and a less circumscribed mass and less tenderness all favor a diagnosis of salpingitis.

3. Appendicitis.

In appendicitis there are no menstrual anomalies, no symptoms or signs of pregnancy, and, usually, no mass.

4. Pelvic tumors.

Ovarian cysts are usually larger than a pregnant tube and less tender, and there is no vaginal bleeding or uterine discharge or change. Small retention cysts are more apt to be confused because they are smaller and more tender; otherwise they have little

resemblance to ectopic pregnancy.

A myoma in the uterine horn rarely causes confusion on account of its history and hardness.

It must be remembered that in all cases of suspected ectopic pregnancy the laboratory hormonal tests of pregnancy should be tried if there is not enough positive evidence from the history and physical examination.

TREATMENT

There probably is less confusion and less divergence of opinion in no other phase of extra-uterine pregnancy than in the treatment. All authors are now agreed that there is no medical management of this condition. As soon as diagnosed the only recourse is to immediate surgery. Every moment wasted hastens the risk and increases the mortality and morbidity. The sooner the surgery the better the prognosis. The technique, time of various procedures, and exactly how the majority of surgeons handle the case will be discussed in this section.

There are several necessary steps to be taken before the patient is taken to the surgery. Her general condition will determine how extensively and completely some of the following preliminary procedures are performed.

If the patient is not in shock, nor has lost an appreciable amount of blood by hemorrhage, in short, if the diagnosis is made before rupture, the task becomes easier for the pre-operative management of these patients as the time element is not the all important factor. Immediate bed rest, warmth and quiet are required to prevent further complications. One may proceed from here to the surgery and technique as outlined below. In general, patients that are diagnosed before rupture may be prepared for surgery as most

other surgical patients. They may enter the hospital several days before the scheduled operation. However, they must be at absolute rest with the avoidance of all strain. The bowels must be clean. A pre-operative enema the evening before the procedure and immediately preceding the operation is desirable. One-fourth grain morphine the preceding evening and one-half grain the morning of the procedure is good sedation. Some use scopolomine, grains 1/150, in conjunction with the morphine, but the possibility of reactions in some individuals does not allow this drug to be given with certainty or safety.

Beginning rupture is a phase in which the immediate intervention and removal of the pregnancy is desired. This phase and its treatment is approximately the same as for frank rupture.

In those cases in which rupture has occurred the surgical management becomes acute. The time element here is all important. However, "operate as soon as possible does not mean ill-timed hurry, but a deliberate, rapid arrangement for surgery, under as favorable conditions as possible (45)." Most of these cases will be in shock or will have lost blood by hemorrhage and would be considered under different circumstances as dangerous operative risks. Therefore, arrangements for infusion and transfusion are made simultaneously with the arrangements for surgery. Rest with sedation, warmth, and shock treatment are necessary measures. It

is wise to remember that when giving fluids to patients that have suffered hemorrhage that the infusion should be given slowly so as not to cause a too rapid rise in the blood pressure and blow out a protecting plug in one of the vessels that has hemorrhaged. The same may be said for gum acacia and other substances used (45).

Technique.

The patient is anesthitized and surgically prepared. Spinal anesthesia is the anesthesia of choice. Inhalation anesthesia may be used. There are two methods of approach, the abdominal and the vaginal.

a. Abdominal approach.

After skin sterilization, a mid-line incision is made. The superficial fascia is incised and the bleeders encountered ligated. The incision line should extend over a wide enough range to allow for complete exposure of the entire pelvis. The deep fascia is encountered and incised. The peritoneum is raised and separated in the usual manner. Upon opening the peritoneum much blood may be encountered. No more blood is removed than is necessary for the proper exposure of the hemorrhaging or ruptured tube. Hemostasis is acquired by digital pressure or by clamps, followed by ligation. The ovary should be rapidly isolated so that it will not be removed with the mass. The removal of the entire tube with a wedge from the

uterine cornu will prevent a second ectopic implantation in the stump of the tube, several cases of which have been reported. The blood should be left in the abdomen as it will be absorbed rapidly, will be of great value to the patient, and will not cause adhesions. For those who are spectacular minded, autotransfusion may be carried out. This consists of removing the old blood, filtering, and transfusing into a vein (51). In early interstitial pregnancy the mass may be removed from the uterus but in more advanced cases a complete hysterectomy may be necessary. The wound is closed with the suture of the surgeon's choice and the patient placed at bed rest until healing intervenes. Subsequent transfusions and general care are of prime importance. The patient has suffered a very drastic operation and should be treated accordingly.

The surgeon who would, while in the abdomen, remove an appendix, or repair any other condition, should be condemmed as all further procedures add to the mortality and morbidity. Never do anymore surgery than is necessary (46).

b. Vaginal removal.

E. Allen (47) of Chicago reports this type removal by way of a case report. The patient entered the hospital and the diagnosis of an unruptured tubal pregnancy was made. A posterior colpotomy incision was made, the tube located and removed. Three years later the same patient entered the hospital with

symptoms and a colpotomy of the opposite side was performed. Another unruptured pregnancy of the tube was removed.

Post-operative complications.

Post-operative complications are frequent in this condition. Langman and Goldblatt (48) record that they had 24 wound infections and 19 pneumonias in a series of 310 operative cases. With careful management complications are reasonably rare. All the complications following any major surgical procedure may be expected.

In the case of abdominal pregnancy there is no immdeiate rush for surgery unless the patient is suffering from a secondary hemorrhage or shock. In these cases, if near term, an operation may be performed to save the life of the fetus although such feti are usually deformed. It is wise to carefully present the case to the mother and to let her decide what shall be done. In those cases past term the fetus is dead, the placenta degenerated and absorbed. Removal of the fetus is desireable.

Posner (49) states that one should always try to save the fetus in abdominal pregnancy. He states that the prime important factor at operation is the removal of the placenta in its entirety. If this is impossible due to its implantation on vital structures, it may be left for absorption without drainage. Cases of chorionepithelioma have been reported

following such a procedure. If the placenta is not removed it may be left to extrude by its own power by an operation known as marsupialization. The membranes are sutured to the wound edge to form a pocket. This establishes a pouch and the structures are left to extrude by pointing to the opening.

MORBIDITY AND MORTALITY

A. Morbidity.

Morbidity as suffered by the patient will quite naturally depend upon the treatment, the time of the treatment, and the skill of the attendent accomplishing the treatment. Woodhouse (29) gives a fairly concise picture of the morbidity as seen throughout the country. "These 73 patients (this series) were in the hospital an average of 18.4 days after operation. The average for those with tubal abortion and rupture was 19 days, and for those with unruptured tubal gestation 16 days. The total period of hospitalization averaged somewhat more than this because of delay in diagnosis in some instances. With the exception of secondary anemia 62 patients had no post-operative complications. Of the remaining 11 (all cases of tubal rupture or abortion) one patient had a severe pyelitis, one had a pulmonary embolus, one ran a febrile course due to an infected hematocoele, one had bronchitis, one had an acute intestinal obstruction necessitating jejunostomy on the fifth post-operative day, three had ileus of a mild degree responding to conservative measures, and two had wound infections."

B. Mortality.

Parry in 1876 reported a mortality of 52.8% in cases with ecchyesis. The reason---"Operative interference is condemned by the highest authorities on

the subject, and he who would subject a woman under these circumstances to the dangers of gastrotomy would have to possess the courage of McDowell and his immediate followers. (4)" Of course with the advent of immediate surgery propounded by Lawson Tait in 1883 the mortality has been markedly lowered. Tait lost only one of 56 operative cases for a percentage of 2.5. Schumann (1), the next author to accurately give a synopsis of the mortality, reports that in 1921 (series of cases for the preceding ten years) in the City of Philadelphia a mortality rate of 3.33% was found.

McDonald reports in a study of 6,626 cases a mortality of 7%. (50).

Woodhouse (29) publishes a list of authors and their mortality rates since 1930. This list is for the ten year period 1930-1940.

Author	Cases	Deaths	Mortality %
Miller	104	7	6.7
Von Graff and Brown	153	3	1.96
Grier	100	3	3.0
Brown	62	1	1.8
Urdan	474	14	2.95
Tyrone et al	309	36	11.6
Koster and Scheinfeld	69	1	1.45
James and Lafferty	103	3	2.91
Meagher	247	8	3.2
Ludwig	145	3	2.0

Author	Cases	Deaths	Mortality %
Scheffey et al	82	4	4.87 #
Fitzgerald and Brewer	500	39	7.8
Ricci and DiPalma	100	9	9.0
Schumann	307	8	2.6
Masson	486	8	1.64 #
Woodhouse' own series	73	1	1.37
	3,314	148	4.46

Two deaths of unoperated cases.

This reduction of mortality compares very favorably with previous reports and is due to the relatively shorter time for diagnosis and a more general knowledge throughout the profession of how to handle shock and hemorrhage. The mortality rate should continue to fall as more physicians are becoming "ectopic minded". This will lead to more accurrate, early diagnoses.

SUMMARY

A. History.

1. First case reported in eleventh century.

2. Next important step in recognition by Cornax in sixteenth century.

3. Operation by Bain in 1540 for long retained fetus. Primerose repeated feat in 1594.

4. Dark period with recognition of no new cases for one century. Riolanus then noted definite forms of extra-uterine gestation. First described tubal form.

5. Mariceau in 1669 gives pathological study of a case of ruptured tubal pregnancy.

6. Ovarian pregnancy discovered by M. de St. Maurice in about 1682.

7. Bard and Baynham in 1790's performed first operations for this condition on this side of the Atlantic.

8. Brechet in 1824 and Dezemeris in 1837 added greatly to scarce literature with their publications.

9. Parry in 1876 published a classic which is quoted today.

10. Lawson Tait in 1883 performed first series of surgical cases with mortality of but 2.5%.Founded our modern treatment.

11. Schumann in 1921 published a monograph which is enlightening and often quoted. A very magnificent work.

B. Etiology.

1. Obstruction of the tubal lumen from without by adhesions, tumors, masses and other conditions which may cause external pressure and close the lumen.

2. Obstruction of the tubal lumen from within usually by a preceding infection. Infectious agent most often gonococcus. Lack of peristalsis of tube musculature, infantile tubes, and tubal insufficiency may lead to ecchyesis.

3. Anomalies of the tubes in which mullerian rests occur, misplaced decidua exists, pseudo-diverticulae are present, or hormonal deficiencies exist have all been propounded as causes.

C. Anatomy and Pathology.

1. Tube made up of three layers. Has gross subdivisions as ampullary, isthmial, and interstitial.

2. Pregnancy most often occurs outside the uterus in the ampullary and isthmial portions of the tube.

3. Implantation columnar or intercolumnar. True decidual formation in tube following implantation is controversial.

4. Tubal and uterine placentae identical in formation.

5. Intraperitoneal rupture most common result of tubal pregnancy. Fetus may develop, mummify, calcify, or suppurate. Tubal abortion may be result of tubal pregnancy. Hematosalpinx and hemorrhage very common.

6. Rupture into broad ligament may occur.

7. Isthmial and cornual pregnancies rupture usually after third or fourth month.

8. Primary abdominal pregnancy questionable.

D. Signs and Symptoms.

1. Menses always shows some sort of disturbance.

2. Pain not a common symptom when localized to pelvis. Some sort of pain usually always present but may be referred to any area of peritoneal irritation.

3. Abdominal tenderness, vaginal tenderness, vomiting and fainting, shock, extreme thirst, chills, or difficult breathing may be present.

4. Cullen's sign rarely present.

5. Shifting dullness present when free blood in abdomen. Shifting pain may also accompany this.

6. Temperature, pulse, and respirations vary as the amount of shock present and the amount of peritoneal irritation.

7. Vaginal examination shows pain when cervix is moved. Softening of cervix, enlargement of uterus, fullness or pulsation in cul-de-sac, or a pelvic mass may be found.

8. Jaundice, discharge of uterine decidua, breast changes, rectal hemorrhage, dysuria, may be found.

E. Diagnosis.

1. A very careful history as to the sequence of

events leading up to the present condition, which should include a detailed account of the menses and pain, is a necessity.

2. A careful, complete physical examination including vaginal and rectal examinations is essential.

3. Blood pressure, red blood count, white blood count, differential blood count, sedimentation time, and the hemoglobin readings are indecies to nothing as they may vary markedly from one patient to the next. The hemoglobin and red blood counts may indicate the amount of anemia present. The white blood count and sedimentation time may indicate the presence of infections.

4. Laboratory, animal hormonal tests of pregnancy are excellent means of determining the presence of pregnancy. The "Frog test" is most simple, accurate, and economical of all.

5. Colpocentesis may be done to determine if there is free blood in the abdomen, but if this procedure is warrented there is enough evidence present to warrant a laporotomy.

6. Curetage is an excellent means of determining whether or not pregnancy exists within or without the uterine cavity.

F. Differential Diagnosis.

1. The most frequent confusing pathological diagnoses are abortion, salpingitis, appendicitis, and

pelvic tumors. They can most easily be differentiated by a careful history, thorough physical examination, and lastly resorting to laboratory aids such as animal hormonal tests for pregnancy.

G. Treatment.

1. There is only one treatment for ecchyesis--- surgical removal.

2. Shock and hemorrhage must be combatted before, during, and following the operation.

3. The abdominal approach is the best as it provides adequate exposure of the pelvis.

H. Morbidity and Mortality.

1. Average hospitalization of patients is 18.4 days.

2. Post-operative complications the same as for any other major surgical procedure where hemorrhage is a complication.

3. Mortality in 1876 was 52.8%. For period 1930 to 1940 the average was 4.46%. The mortality rate should continue to drop if physicians become "ectopic minded" and make quicker diagnoses.

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