Surgical management of tubal pregnancy
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Introduction and outline of the thesis
Ectopic pregnancy is an early pregnancy complication in which a fertilized ovum implants outside the uterine cavity. Implantation may occur anywhere along the reproductive tract with the most common implantation site being the fallopian tube. Apart from a previous tubal pregnancy, one of the most important risk factors for tubal pregnancy is presented by genital Chlamydia Trachomatis infection which may lead to pelvic inflammatory disease, thereby causing tubal damage (1).

TRYING TO UNDERSTAND THE TUBAL PREGNANCY: THE PRE MODERN ERA

The first known reference to ectopic pregnancy appears in writings of the Arabic physician Albucasis in Spain (936-1013). In his case report, the fetal parts were discharged from the abdomen through the umbilicus after the death of the fetus (2, 3). Although the fallopian tubes were named after Grabrielis Fallopius (Italy, 1523-1562), an Italian anatomist who described these structures for the first time, the association with tubal pregnancy was only recognised much later (4). It took until 1669, when Benoit Vassal, a surgeon in Paris, was the first to describe the location of a tubal pregnancy which showed the dawning of an anatomically correct concept of the disease. He performed an autopsy on a woman who died of intra-abdominal haemorrhage due to a ruptured ectopic pregnancy. In a report to the Royal Society of London, Vassal described the clinical history and presented his famous anatomical plate derived from his autopsy findings:

“…..the brother yet a featus was conceived in an adjunct uterus, in a place so little capable of distension, that seeking enlargement, after it had caused to the mother for two months and an half grievous symptoms, did at last, being at the age of about 3 or 4 months, break prison, and found its grave in that of his mother; which cast the mother into such violent convulsive motions for 3 days together, that she died of them” (5).

Although Vassal must have known about the fallopian tubes as described by Fallopius, he did not recognize these as being the location of the ectopic pregnancy and misjudged the tube as an adjunct uterus.

The prominent Dutch physician Reinier de Graaf (1641-1673) was the first to understand the reproductive function of the Fallopian tube. De Graaf examined the reproductive tracts of rabbits and humans with low power microscopes, and distinguished normal tubes from diseased ones(tubes) (hydrosalpinx), described tubal pregnancy thereby also expressing his thoughts on the relationship between tubal pathology and female infertility. De Graaf commented to the case report of Vassal in a letter to the Royal Society of London and explained his views on the pathophysiology of tubal pregnancy. De Graaf explained:
“All these cases prove that the eggs from which fetuses are to be generated pass from the ‘testicles’ through the tubes to the uterus and that a fetus is generated in a tube from no other cause than that an already fertilized egg gets caught for some reason or other in its transit. As such a fetus grows it prepares death for its mother.”

The view of de Graaf must have been revolutionary since it challenged the general belief at that time that the function of the tube was to let the fetus breathe inside the uterus. De Graaf was already aware that “the fetus has no need to breathe at all since this was the function of the placenta.” Unfortunately, de Graaf died at the age of 32 of an unknown cause. It is a misfortune, that de Graaf could not take advantage of the work of his close friend Antonie van Leeuwenhoek, a Dutch drapery trader and scientist, who developed powerful lenses and invented the high power microscope just after De Graaf’s death (6). This instrument would have enabled De Graaf to study human procreation in greater detail. Despite the correct understanding by De Graaf of the function of the tube (oviduct) as being the location of most ectopic pregnancies, making the correct diagnosis remained difficult. Until the 18th century, ectopic pregnancy inevitably led to maternal death. Treatment at that time was directed at killing the fetus rather than stopping the ruptured tube from bleeding. The therapeutic arsenal included starvation, purging and bleeding of the mother, administration of strychnine, passage of electromagnetic, galvanic or Faradic currents through the ectopic mass and injection of morphine into the fetal sac (7, 8). Whatever the treatment, the prognosis was poor; the maternal mortality rate was between 72% and 99% (9).

THE FIRST SURGICAL ATTEMPTS: 18TH AND EARLY 19TH CENTURY

The first few case reports describing surgical treatment of ectopic pregnancy appeared in the United States. In 1759, John Bard from New York was the first surgeon to successfully operate on an abdominal pregnancy (10, 11). In 1791, the second successful operation was performed by William Baynham, a country physician from Virginia (12). In the 30 abdominal operations that followed only five women survived. In contrast, the survival rate in women not operated upon was much better. Reasons for this lack of success of surgical treatment were the difficulty of establishing a timely diagnosis, as a consequence of which women were already in hypovolemic shock at the start of surgery. In 1849, W.W. Harbert of Louisville, Kentucky, was the first to suggest surgery early enough to stop fatal bleeding (13). Moreover, the lack of general anaesthesia, sepsis and the inability to treat hypovolemic shock with blood transfusions attributed to the low survival rate after surgery.
DISCOVERIES ALLOWING SURGERY: LATE 19TH AND EARLY 20TH CENTURY

General anaesthesia and the control of pain and antisepsis allowed the transition to modern surgery.

General anaesthesia and the control of pain

It took until 1842 when significant advances in pharmacology and physiology led to the development of general anaesthesia and the control of pain. In 1842, the American surgeon and pharmacist Crawford Williamson Long (1815-1878) used ether for the first time to remove a neck tumour and as an anaesthetic in amputations and childbirth (14). William Thomas Green Morton (1819-1868), an American dentist, was unaware of the use of ether by Long and demonstrated in 1846 the use of inhaled ether as a surgical anaesthetic before a medical audience at the Massachusetts General Hospital in Boston, Massachusetts. News of his use of ether spread rapidly around the world. Two months later the first recorded use of ether in Britain took place on December, 21st 1846 by Robert Liston (1749-1847), a Scottish surgeon at University College Hospital London (15). Anaesthesia and pain control made it possible for surgeons to operate longer albeit with an increased risk of infections.

Antisepsis

The foundation for the germ cell theory of diseases and antisepsis had already been laid by Antonie van Leeuwenhoek (1632-1723). He was the first to observe single cellular organisms through his high power microscope and is therefore considered the first microbiologist. De Graaf, instead of van Leeuwenhoek himself, wrote the journal’s editor Henry Oldenburg with a ringing endorsement of Leeuwenhoek’s microscopes which, he claimed, “far surpass those which we have hitherto seen”. Three months after the death of De Graaf in 1673, van Leeuwenhoek himself wrote his first of many letters to the Royal Society about his observations. However, the discovery of these single cellular organisms was not yet linked with the clinical presentation of infectious diseases.

In 1847, –170 years after the discovery of micro-organisms by van Leeuwenhoek- Ignaz Semmelweis, a Hungarian obstetrician in Vienna, recognized that puerperal fever was in fact a contagious disease. He observed a dramatically high maternal mortality rate of 18%. Semmelweis related the death of these women to the autopsies performed by the doctors who also assisted the deliveries. Without knowing the exact matter of micro-organisms, Semmelweis introduced antisepsis by insisting on doctors to wash their hands with chlorinated lime water before examining pregnant and puerperal women, thereby reducing the mortality rate to 2.2%. Semmelweis’s hypothesis, that there was only one cause, that all that mattered was cleanliness, was extreme at the time, and was largely ignored, rejected or ridiculed. Semmelweis’s practice earned widespread acceptance only years
after his death, when Louis Pasteur between 1860 and 1864 developed the germ theory of disease, offering a theoretical explanation for Semmelweis’s findings. He discovered the pathology of the puerperal fever and the pyogenic vibrio in the blood, and suggested using boric acid to kill these micro-organisms. Later Robert Koch (1843-1910) gave experimental support for the concept of infectious disease and was rewarded with the Nobel Prize in Physiology or Medicine in 1905. The appreciation of the germ theory of disease led rapidly to the development and application of antiseptic techniques in surgery. Joseph Lister (1827-1912), a surgeon from London introduced the use of carbolic acid (phenol) as antisepsis to disinfect skin, the hands of surgeons and catgut. Antisepsis reduced the overall morbidity and mortality of surgery to a far more acceptable rate than in previous eras.

THE PIONEERS IN SURGERY: LATE 19TH AND EARLY 20TH CENTURY

Developments in the USA and UK

Robert Lawson Tait (Scotland, 1845-1899) was known for the first ovariectomy which he performed in 1867. In 1871 he was one of the founders of the Birmingham and Midland Hospital for Women where he performed the first appendectomy in 1880. His surgical successes resulted partly from his ‘aseptic’ techniques. He did not agree with Lister’s use of carbolic acid for antisepsis and changed to asepsis by using soap and water to wash his hands thoroughly, instruments were boiled, linen laundered, small incisions were used and postoperatively he removed excess blood from the abdomen and used a peritoneal ‘wash-out’ with boiled water. Although he used ether and opium for anaesthesia and control of pain, the operations were performed as fast as possible to reduce the risk of infection.

In 1872, he performed his first vaginal section of an ectopic pregnancy; which was not successful. It is worth noting that safe transfusion of large volumes of blood was not available.

“Vaginal examination revealed a tumour behind the uterus, occupying the whole available space, immovable, and with a peculiar boggy feeling to the touch. On examination by the rectum I felt what I believed to be the knee of a child and the edge of the placenta. In this case the temptation to remove the child through the vagina was very great, if a mere notch in the mucous membrane and the child would come..................With torn vessels bleeding it is simply hopeless to expect to be able to find them and secure the bleeding.” (16)

After this unsuccessful case, Tait stated that vaginal section should invariably give way to abdominal section. In 1873, he performed the first laparotomy to remove a full-term, extra-uterine fetus and developed the technique of leaving the placenta in situ to reduce the risk of haemorrhage. In case of unruptured tubal pregnancy, he drained the ectopic sac by stitching the sac with the omentum to the 3 inch wide incision of the abdominal wall and let it open for 10 to 14 days (17). It is unclear to which extent this type of surgery was used
by others, but from the critical letter he wrote to the British Medical Journal in 1882, it can be concluded that “the doing nothing policy” was used by many colleagues. Tait criticized his colleagues “on the obstructive attitude which is maintained by a large number of my professional brethren against the progress of abdominal surgery” (17). Tait was inspired by the work of John S. Parry of Philadelphia, who also called these women “inevitably doomed to die, unless some active measure wrest her from the grave” (11, 16).

For women with tubal rupture, Tait did not have a solution yet. In fact, Parry was the first to suggest that the only remedy would be to open the abdomen and tie the bleeding vessels and to remove the sac entirely (11). In 1881, Dr. Hallwright, a general practitioner from London, presented a woman with tubal rupture, and suggested Tait to perform a laparotomy and to remove the ruptured tube to stop the bleeding. Tait did not do so and the woman died. Tait later wrote “... the suggestion staggered me, and I am ashamed to say that I did not receive it favourably” (16). A post-mortem examination convinced him that appropriate dissection and ligation of bleeding vessels would have been effective in the treatment of the tubal pregnancy. He performed his first operation for a ruptured tubal pregnancy in 1883. “As well as I could I stitched the edges of the rent to the abdominal wall, but every touch caused haemorrhage”. The patient died shortly afterwards. In the next patient with suspected tubal rupture he successfully tied the ruptured tube and removed it (18). By 1885, Tait had accumulated a relatively large number of successful cases of salpingectomies by laparotomy (16). According to Tait, the diagnosis of a tubal pregnancy remained difficult, but if recognized, the procedure of choice was a laparotomy before rupture.

In 1913 it is stated in Hartmann’s textbook that: “every ectopic when diagnosed should be operated upon”. Expectant management led to death in 86%, but surgery saved 85% of women (8).

Developments in The Netherlands

The mainstream treatment in The Netherlands between 1887 and 1897 was a laparotomy with removal of the tube with the ectopic sac and usually combined with the removal of the ovary or even a supravaginal hysterectomy (19). Klaas de Snoo, assistant to Benjamin Jan Kouwer, professor in Obstetrics of the University of Utrecht, questioned the need for laparotomy in hemodynamically stable women with suspected tubal pregnancy (20). He introduced conservative management in these women and reserved laparotomy for those women who developed severe clinical symptoms of tubal rupture. Hector Treub (1856-1920), professor in Obstetrics of the Women’s Clinic of the University of Amsterdam, held the opposite opinion. In the first edition of his textbook of Obstetrics, he stated that laparotomy should be performed in all women with suspected tubal pregnancy (19). In case tubal rupture had already occurred, as indicated by strong abdominal pain, syncope and a weak pulse, only then conservative management was justified according to Treub, because he observed that if women died it was always within the first few hours after rupture. If women survived these hours, Treub concluded that the flow of blood had been constricted.
To keep the flow of blood constricted, women had absolute bed rest with a low hanging head, an ice pack on the abdomen combined with repeated internal admissions of opium. After a few days, the ice pack was removed and replaced by a Priesnitz bandage (hydrotherapy as an alternative medical method). The opium was no longer administrated and hot vaginal irrigation (45°C Celsius) was applied. This conservative approach for tubal rupture was not shared by other gynaecologists. To support his approach, Treub started together with his assistant Johanna van Kesteren, a nationwide study on the outcome of women with tubal rupture (21). The mortality rate in this study including 331 women was 12.6%. Indeed most women died immediately after collapse, thus surgery was anyway too late. Because of this controversy between Treub and Kouwer a special committee was appointed by the Dutch Society of Obstetrics and Gynaecology. In an annual meeting in 1909 these major differences in clinical practice were profoundly discussed but a consensus was not reached (22). Again Treub together with van Stockum both advised against laparotomy in case of suspected tubal rupture. Van Stockum admitted that the prognosis of surgical management in general markedly improved because of asepsis but blood transfusion was still not available. For women with unruptured tubal pregnancy the general opinion was to perform a laparotomy. Kouwer was the only gynaecologist who did not approve because he observed many laparotomies where no tubal pregnancy was found. Treub did not regard this as a problem since usually other pathology was found necessitating surgery, such as ovarian cysts. It took until 1929 when Professor van Rooy, successor of Treub abandoned the conservative approach and started to do emergency laparotomies in case of suspected tubal rupture. He stated that previous dangers of surgery and other objections of previous years, such as infection and the limited ability of transportation of the patient to the clinic, could no longer dictate clinical practice (23).

SURGERY AS A MAINSTREAM PROCEDURE: MID 20TH CENTURY TILL PRESENT

Blood transfusion

The introduction of blood transfusion further decreased maternal mortality from tubal pregnancy. Already in 1818, the British obstetrician Dr. James Blundell performed the first successful transfusion of human blood to treat postpartum haemorrhage. Blundell used the patient’s husband as a donor, and extracted four ounces of blood from his arm to transfuse into his wife. The first auto transfusion was performed after amputation of a leg in the United Kingdom in 1886 (24). In ruptured tubal pregnancy, auto transfusion, or salvage and re-infusion of shed blood, had been used sporadically since 1914 when Theis, a German obstetrician, successfully returned blood through a gauze filter in three women (25). However, multiple problems with blood hampered its regular use. Blood was difficult to handle because of its rapid clotting time, which effectively eliminated even temporary
storage and indirect transfusion. Lethal transfusion reactions were not understood until 1901 when Karl Landsteiner discovered the ABO blood type system. It took him until 1939 when he discovered the Rhesus blood type system. In 1941, during the second World War, the Red Cross started the first blood donor service. After blood typing and cross matching became widely spread, blood transfusions became more safe and widely used. From then onwards, laparotomy with salpingectomy combined with autologous or allogeneic blood transfusions became the mainstream treatment.

Concept of non ablative surgery

In 1920, Beckwith Whitehouse in the United Kingdom raised the question as to whether sacrificing the tube on all occasions was justified. He performed a salpingotomy first in fresh specimens after salpingectomy. Thereafter, he introduced the method on five occasions and reported these to be successful in 1921. He stated:

“Time, of course, must prove whether the adoption of such a procedure is followed by other complications such as the recurrence of the accident, the development of hydrosalpinx, or, perchance the incidence of a tubal chorion-epithelioma” (26).

He did not mention future fertility. The first instance of conservative surgical treatment for tubal pregnancy, i.e., salpingotomy, which appeared in the English literature, was published in 1953 from Minneapolis, USA (27). The argument in favour of conservative surgery was preservation of the childbearing function confirmed by subsequent successful pregnancies. From 1957 onwards, this concept of preservation of the affected organ was propagated over ablative surgery in view of future reproductive capacity (28). Treatment had shifted from the saving of lives to the preservation of fertility. Although randomised studies were lacking, salpingotomy was widely adopted, assuming a positive effect on reproductive outcome, while accepting the potential drawback of a repeat tubal pregnancy in the same tube (29). Patrick C. Steptoe, pioneer in laparoscopy and later known for the first tubal pregnancy (30) and the first live birth after IVF (31), in the first textbook of Laparoscopy in Gynaecology stressed the importance of making an early diagnosis by laparoscopy to preserve the woman’s future fertility prospects:

“When the patient wishes at all costs to conserve the possibility of a future pregnancy, it may be vital to her that the diagnosis is made before tubal rupture. Not only gross damage to the tube may be avoided, together with the risk of dangerous haemorrhage, but also restorative surgery on the tube is much more likely to be successful” (32).

From the 1970s onwards, laparotomy was gradually replaced by therapeutic laparoscopic options. In 1973, Shapiro and Adler in Norwalk, Connecticut, USA reported laparoscopic salpingectomy using electrocoagulation followed by excision for a tubal pregnancy (33). Salpingotomy by laparoscopy was first reported using multiple punctures in 1980 in Clermont-Ferrand, France (34). Linear salpingotomy with a cutting current with Wolf hook scissors was
described by DeCherney et al. in 1981 at Yale University, New Haven, Connecticut, USA (35). In 1984, Richards in Lakewood, Colorado USA reported another drawback of salpingotomy; the incomplete removal of the pregnancy, i.e. persistent trophoblast, necessitating additional treatment for which at that time additional surgical treatment (salpingectomy) was necessary (36).

**CURRENT PRACTICE AND GUIDELINES**

The former clinical picture of tubal pregnancy as a life-threatening disease has changed into a more benign condition in women who are frequently asymptomatic or show a mild clinical picture dominated by vaginal bleeding and/or slight abdominal discomfort. This is the result of sensitive diagnostic tools, together with an increased awareness among both the public and health care providers. The Dutch Society of Obstetrics and Gynaecology issued an evidence-based guideline on diagnosis and management of ectopic pregnancy. (37). Three recommendations in this guideline were derived from previous theses of the Ectopic Pregnancy Research Group. One recommendation was the use of a diagnostic algorithm integrating transvaginal sonography, serial serum hCG measurements and time to make a correct and timely diagnosis, thereby optimizing fertility prospects (38, 39). Another recommendation was the use of medical treatment with systemic methotrexate in selected women with ectopic pregnancy with low serum hCG levels (40). The third recommendation was to perform salpingotomy in women with tubal pregnancy and contralateral tubal pathology and a wish to conceive again. In women with a normal contra lateral tube during surgery, no preference for either salpingotomy or salpingectomy was recommended in the absence of clinical evidence (41).

These recommendations were quoted in the original and updated “Greentop guideline 21: the management of tubal pregnancy” of the Royal College of Obstetricians and Gynaecologists. (42) The National Institute for Health and Care excellence (NICE) issued a guideline on Ectopic Pregnancy and Miscarriage (43). NICE recommends to offer a salpingectomy to women undergoing surgery for a tubal pregnancy unless they have other risk factors for infertility and to consider salpingotomy as an alternative to salpingectomy for women with risk factors for infertility such as contra lateral tube damage.

**BACKGROUND OF THIS THESIS**

When we started the studies described in this thesis, an epidemic of genital Chlamydia Trachomatis infection among young women in The Netherlands was reported (44). To study the magnitude of the problem of tubal pregnancy in The Netherlands, we performed a population based study to explore whether changes in the incidence pattern of Chlamydia and pelvic inflammatory disease have had an impact on the incidence of tubal pregnancy in
The Netherlands in a 25-year period. In addition, we investigated whether we can expect a trend change in the incidence of tubal pregnancy in The Netherlands in the near future due to changes in demography, life style or sexual behaviour.

Although the national guideline was available since 2001, summarizing the existing evidence for diagnosis and treatment for tubal pregnancy, it was well recognized that implementation of evidence-based guidelines in general is often problematic in daily practice (45-47). It was unknown to what extent the recommendations from the guideline, especially of the diagnostic algorithm to get a timely diagnosis, were implemented in Dutch clinical practice. To answer this question, we developed a set of quality indicators. These indicators were then used to assess the quality of actual care for women with tubal pregnancy and to measure the adherence to the guideline from 2003 to 2005.

When tubal pregnancy is timely diagnosed, the full range of treatment options is available. This wide spectrum was already summarized in a Cochrane systematic review and meta-analysis in 2000 holding 22 various comparisons (48). After the publication of the Cochrane review, more studies were published on treatment combinations or new regimens. From this wide spectrum we aimed to summarize evidence, focusing on clinically relevant interventions which were useful for daily practice. We therefore planned a systematic review and meta-analysis to evaluate the effectiveness of surgery, medical treatment and expectant management of tubal pregnancy in terms of treatment success (i.e. complete elimination of trophoblastic tissue), financial costs and future fertility.

From the guideline and the systematic reviews an apparent evidence gap was recognized in the field of surgical management; the two commonly used interventions had not been evaluated and a randomised controlled trial was desirable. These interventions were conservative surgery by removing the ectopic pregnancy only and thus saving the tube for future reproduction (salpingotomy) or radical surgery by removing the tube including the ectopic pregnancy (salpingectomy) leaving only one tube for future reproduction. Salpingotomy preserves the tube, but bears the risks of both persistent trophoblast and repeat ectopic pregnancy. Salpingectomy, minimizes these risks, but leaves only one tube available for future reproduction. In view of this trade off and evidence gap, we started a randomised controlled trial to study the impact on future fertility in women with tubal pregnancy and a normal contralateral tube.

Salpingotomy was expected to be more costly than salpingectomy because of higher financial costs for the treatment of persistent trophoblast and repeat ectopic pregnancy. To study the impact of salpingotomy and salpingectomy on financial costs, we performed a cost effectiveness analysis (CEA) alongside the randomised controlled trial.
Apart from clinical outcomes and costs, we regarded patients’ preferences of importance in clinical decision making. In the field of surgical treatment of tubal pregnancy, patients’ preferences were not known. The question was whether women feel that a possibly better fertility outcome after salpingotomy as compared with salpingectomy outweighs the risk of persistent trophoblast and repeat ectopic pregnancy. Discrete choice experiments (DCE) were increasingly used in health care as an approach to elicit patient preferences (49-51). To study women’s preference for salpingotomy relative to salpingectomy, we performed a patient preference study by means of a discrete choice experiment in women surgically treated for tubal pregnancy and subfertile women desiring pregnancy.

**OUTLINE OF THE THESIS**

In **chapter 2** we report on time trends in the incidence of tubal pregnancy. We studied to which extent the changes in the incidence of genital Chlamydia Trachomatis infection and pelvic inflammatory disease had an impact on the incidence of tubal pregnancy.

In **chapter 3** we describe the adherence to the Dutch Guideline on Management of Tubal Pregnancy. We developed a quality indicator set and measured actual care in women with ectopic pregnancy in six hospitals in The Netherlands.

In **chapter 4** we give an overview of the current evidence on surgery, systemic methotrexate and expectant management in the treatment of tubal pregnancy in a systematic review and meta-analysis.

In **chapter 5** we report the results of a randomized controlled trial of salpingotomy versus salpingectomy in women with tubal pregnancy and a normal contralateral tube and the impact on subsequent fertility. The primary outcome measure was ongoing pregnancy by natural conception. Secondary outcomes were persistent trophoblast and repeat ectopic pregnancy.

In **chapter 6** we report the results of the cost-effectiveness study which was performed alongside the randomized controlled trial of salpingotomy versus salpingectomy.

In **chapter 7** we describe a patient preference study on salpingotomy or salpingectomy. Using a discrete choice experiment, we assessed how the negative impact of additional systemic methotrexate treatment for persistent trophoblast and the negative impact of repeat ectopic pregnancy were valued against the positive impact of an intra-uterine pregnancy.

**Chapter 8** presents the summary of this thesis and provides suggestions for future research in tubal pregnancy.
REFERENCES


44. van der Bij AK, Geskus RB, Fennema HS, Adams K, Coutinho RA, Dukers NH. No evidence for a sustained increase in sexually transmitted diseases among heterosexuals in Amsterdam, the Netherlands: a 12-year trend analysis at the sexually transmitted disease outpatient clinic, Amsterdam. Sex Transm Dis 2007;34:461-7.


