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Reinier De Graaf (1641–1673) and the Fallopian tube

W.M.Ankum[1,3], H.L.Houtzager[2] and O.P.Bleker[1]

[1]Department of Obstetrics and Gynecology, Academic Medical Center, Amsterdam and [2]Department of Obstetrics and Gynecology, Reinier de Graaf Gasthuis, Delft, The Netherlands

TABLE OF CONTENTS

Introduction

The 17th century Dutch scientist Reinier De Graaf (1641–1673) is generally regarded as the founder of modern reproductive biology (Setchell, 1974). His name is associated with the ovarian follicles which, in honour of his achievements, were named after him. De Graaf is known in particular for his scientific work on the reproductive organs. His monograph on the male reproductive system was published in 1668: 'tractus de virorum organis generationi inservenientibus' (De Graaf, 1668). Some 4 years later, in 1672, his work on the female genital tract was published, which contained the famous description of the ovarian follicles: 'de mulierum generationi inservenientibus tractatus novus' (De Graaf, 1672).

Although De Graaf had never actually seen spermatozoa (the high power microscope was invented shortly after his death by his fellow countryman Antoni Van Leeuwenhoeck in 1677), he achieved a deep understanding of human procreation. Many of our present views remain the same because they are rooted in his work.

Although the Fallopian tubes were named after Gabrielis Fallopius (Italy, 1523–1562), who described these structures for the first time, Reinier De Graaf was probably the first to understand their true function. This matter is the subject of the present paper.

The original work of Reinier De Graaf was published in Latin and Dutch (De Graaf, 1668, 1672, 1686). Here we use a series of quotations from the English translation of the original Latin text by Jocelyn and Setchell (1972).

[3]To whom correspondence should be addressed

Misinterpreted 16th and 17th century anatomy

The pioneer of modern anatomy, Andreas Vesalius (1514–1564), considered the uterine tubes to be analogous to 'semen-conveying ducts' or ductus deferentes of the male. He described them as being attached to the ovaries, thus reflecting the old interpretation of Galenus (AD 130–201) (Herrlinger and Feiner, 1964). It was his main pupil, Gabrielis Fallopius, who was the first to describe the tubes more accurately (Fallopius, 1561, in Medvei, 1982):

> 'That slender and narrow seminal passage arises from the horn of the uterus very white and sinewy but after it has passed outward a little way it becomes gradually broader and curls like the tendrils of a vine until it comes near the end when the tendril-like curls spread out, and it terminates in a very broad ending which appears membraneous and fleshy on account of its reddish colour. This ending is much shredded and worn like the fringe of a worn piece of cloth and it has a broad opening which always lies closed by the coming together of those fringed ends. However, if they are opened carefully and spread apart, they form, as it were, the bell-like mouth of a bronze trumpet. Consequently since, whether the tendril-like curls be removed from the classical instrument or even added to, the seminal passage will extend from its head even to its uttermost ending and so it has been designated by me the trumpet (tuba) of the uterus.'

Although Fallopius' anatomical description of the tubes was accurate, the understanding of human reproduction remained confused, as is clearly illustrated by the anatomical viewpoints of Riolan, published in 1618. This renowned French anatomist assumed the ovarian ligaments to be the oviducts, which he mistakenly thought to be connected to both tubes and uterine arteries.

> 'From the bottom extremity of the testicle there grows a small vessel, hard, white, very thin and with the length of the little finger. It implants itself in the fundus of the uterus near where the tube inserts itself. This is the ejaculatory vessel. Inside the tube of the uterus, however, there is another small, nervous, oblong, white body, which is a continuation of the ejaculatory vessel itself. The two bodies

join together in the fundus and pour semen from their extremities into the cavity of the uterus. They also produce from their root a small, thin, extremely tortuous runner, which traverses the uterus laterally and continues to the true cervix of the uterus.'

This misinterpretation of female anatomy was generally adapted by other illustrious anatomists of that time because it suited the contemporary theories on procreation. The female semen — thought to contain a spiritual and a liquid part — could be disposed of through the tortuous runner (actually the uterine artery) whenever the transuterine route was blocked by a pregnancy.

De Graaf's view

In the chapter concerning the 'delivering vessels of women, or rather their oviducts', Reinier De Graaf addressed the anatomical perceptions of that time, which he firmly denied (De Graaf, 1672). He wrote:

'... accurate investigation of the genital parts suffices to upset the theories of these very famous men and establishes that there is no such duct as Fernel, Du Laurens and others describe. We do not know what deceived them unless it were the spermatic arteries.'

In response to the findings of Riolan, he stated:

'Neither are there to be found the ducts which according to Riolan go off the tubes of the uterus. Riolan may have mistaken the ramifications of the spermatic arteries running to the tubes for these ducts.'

De Graaf described the Fallopian tubes as follows:

'"The trumpets", or "tubes", [...] are two in number, one on either side. In human females they are situated at the sides of the uterus. Where they originate, at the fundus, they are quite narrow, as one can see in Plates X and XIX (Figure 1). As they pass through the substance of the uterus and for some distance outside they proceed in a straight course, gradually widening. When, however, they have attained an appreciable size, they curve perceptibly more and more and proceed, bending from side to side or twisting like vine-tendrils. In this way they get half way round the 'testicles' at a distance from them. At their ends, however, where they are widest, they gather together again. The parts which extend beyond where they gather together split into many particles and terminate in fringes reminiscent of the leafy ornamentation we call "loof-werck". The very elegant shape of this ornamentation can be seen if it is placed in water and examined with the aid of a microscope or some other device.

In this leafy ornamentation of the tubes hydatids sometimes develop. We have also seen very hard calculi adhering to individual extremities of the ornamentation and still preserve them together with the ornamentation.

In cows, ewes, rabbits and other animals the tubes originate in the horns of the uterus. Their extremities do not split as they do in human females but expand into

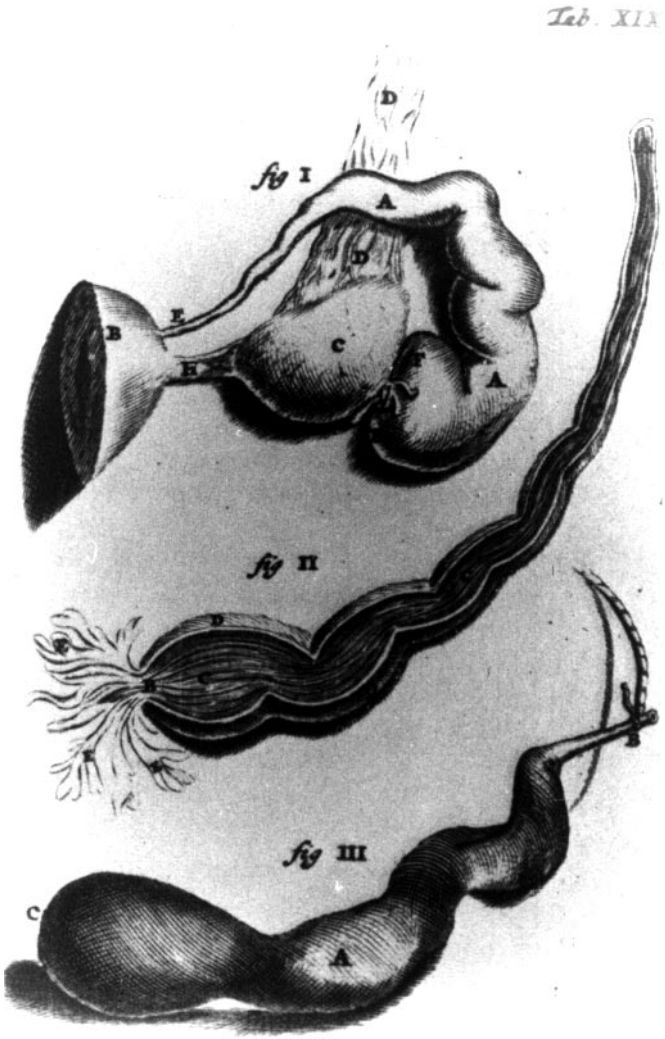

Figure 1. Plate XIX from *De Mulierum Organis Generationi Inservenientibus*. Top: fig I displays an abnormally arranged oviduct, where the end of the oviduct is abnormally stuck to the 'testicle'. The small aperture in the end of the oviduct veiled all around with very leafy ornamentation. Middle: fig II displays an oviduct opened lengthwise. Bottom: fig III displays an oviduct, the end of which we found abnormally closed after being inflated.

continuous very thin membranes and terminate in practically the same way as do the oviducts in fowls. [...]

We said that the tubes gather together at their extremities but do not close. In the normal order of Nature they are always gathered together to a noteworthy degree; in abnormal circumstances, however, they are sometimes completely closed. Plate XIX (fig 1) gives an example of this. We believe that those who have written that the tubes are always closed happened upon a misfortune of this kind. This is why Fallopia also, who in his Institutiones wrote that they are closed, afterwards in his Observationes, when he was better informed, covered up his error, saying that their pervious apertures are closed by the fringes falling together. It must accordingly be stated unreservedly that the tubes are pervious.'

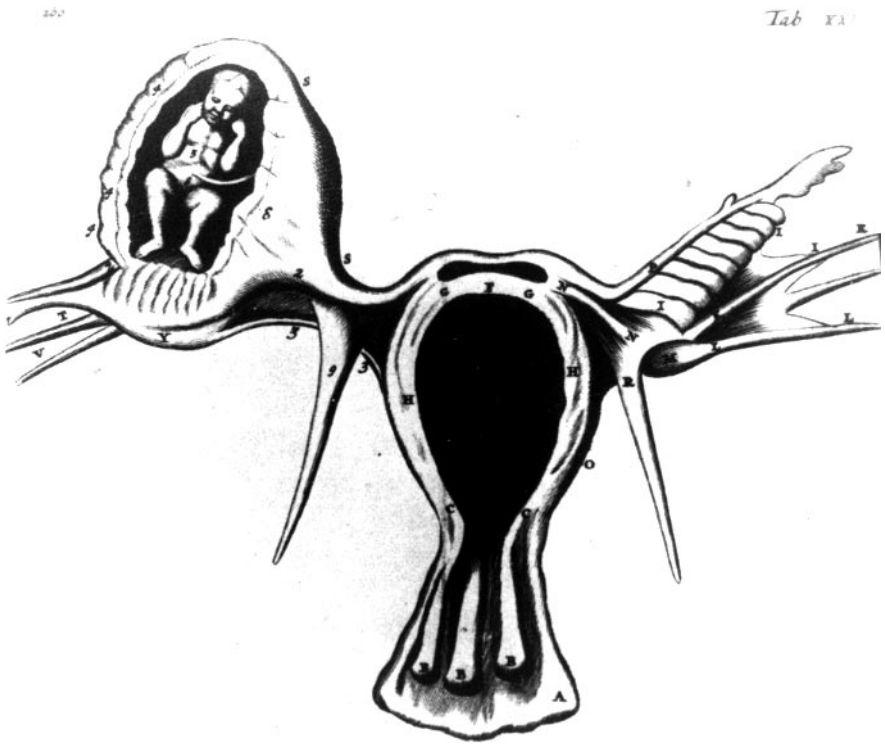

Figure 2. Plate XXI from *De Mulierum Organis Generationi Inservenientibus*, which De Graaf reprinted from Vassal's report to the Royal Society. A = part of the vagina; B = the inner orifice of the opened uterus; C = the cervix; D = the cavity of the uterus; E = the line dividing the cavity of the uterus; F = the fundus; G = two hollows found in the fundus of the uterus; HH = the thick wall of the uterus; II = the broad ligament, or extension from the left side of the peritoneum, containing within its fold the deferent and ejaculant vessels; K = the spermatic artery; L = the spermatic vein; M = the 'testicle'; N = the true ejaculatory vessel which inserts itself into the fundus through the hollow there; O = the second ejaculatory vessel which enters the cervix; by means of this vessel women ejaculate after they have conceived; P = the tube of the uterus; R = the round ligament; S = the broad ligament on the side where the false uterus we are talking about was formed; T = the spermatic artery (of the right side); V = the spermatic vein; Y = the 'testicle'; Z = part of the tube; 2 = the true ejaculatory vessel, which enters the fundus through the above mentioned hollow; 3 = the second ejaculatory vessel passing into the cervix; 4 = part torn by the growth of the fetus; 5 = the fetus in the position where it was found, wrapped in its amnion; 6 = the umbilical vessels; 7 = the placenta adhering to a fleshy substance; 8 = the fleshy substance; 9 = the round ligament. Note that this explanation of the figure was given by Vassal; if we were permitted to interpret it, we should explain the following letters like this: GG = a blood vessel opened lengthwise; nn = the ligaments of the 'testicles' regarded as ejaculatory vessels; o = a blood vessel traversing the side of the uterus; ss = the dilated Fallopian tube or oviduct, in the cavity of which the fetus was found; 2 = the lower part of the tube; 3 = the blood vessel of the other side of the tube running to the uterus; 5 = the fetus found in the tube.

Obviously, De Graaf understood very well the essential difference between the normal open (pervious) tube and abnormal closed tubes. Therefore, his plate XIX (Figure 1) may be considered to be the first well understood illustration of tubal abnormality in history.

Reinier de Graaf assumed the ovaries to be the origin of female gametes, and in fact believed the ovarian follicles to be the ova. From his observations in human anatomy and from his experiments in rabbits, De Graaf had observed that:

> '... not only do the expansions at the ends of the tubes embrace the 'testicles' from all sides but, in rabbits, the eggs themselves on the 3rd day after coitus can be seen to pass through the tubes.'

De Graaf clearly understood the analogue function of the human Fallopian tubes, but obviously the problem was how to prove this. To make his point, Reinier De Graaf used the clinical picture presented by tubal pregnancy, which he knew of from several case reports in literature. De Graaf quoted an account from the *Transactions of the Royal Society* (of London), which stated:

> 'This figure (Figure 2) represents the two matrixes, found januar. 6 1669 by Benoit Vassal, Chirurgeon, opening the body of a woman of 32 years of age, of a sanguin constitution, and a masculin port. These two matrixes were so well disposed by an extraordinary contrivance of nature, that the true one had conceived eleven severall times, viz. 7. males and 4. femals, all born at the full time, and all perfectly wellform'd; but they were at last follow'd by a

> brother yet a faetus, that was conceiv'd 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 its mother, by a very great effusion of blood in the whole capacity of her abdomen; which cast the mother into such violent convulsive motions for 3 days together, that she dyed of them. Whereupon the said Vassal, after having embalmed her parts, he had made at his house for a whole month together the particular dissection thereof, before all the most curious and knowing physicians, chirurgeons, apothecaries, mid-wifes, and other searchers of nature, that are in Paris, thought good to preserve the history thereof by committing and the figure of the parts spoken of, to press, together with a table, for better explanation; which we think fit here to annex in Latin.' (Philosophical Transactions, 1668; De Graaf and Israel, 1963–1964)

De Graaf also added the comment to this case report, written by Henry Oldenburg (Oldenburgius, 1615–1677), the Royal Society's secretary and editor:

> 'It may be, that, which is by M. Vassal, publisher of this relation, esteem'd a second womb, is nothing else, but the true Matrix lengthen'd, or that, which by anatomists is call'd Tuba Fallopii. See *Bartol. Anatom. Reform.* I. 1.c.27. and others.'

Obviously, De Graaf shared Oldenburg's view, and made his point by concluding:

> '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 cought for some reason or other in its transit. As such a fetus grows it prepares death for its mother.
>
> This theory of ours also makes it easy to explain how fetuses sometimes develop in the cavity of the abdomen among the intestines. Fertilized eggs fall from the 'testicles' outside the cavity of the tubes, are fostered by the adjacent parts and increase in size until, with the help of a placenta, they become joined to these parts and attain their ultimate perfection. None of this can be readily explained otherwise.
>
> A further point is that, if the tubes were not designed for the purpose suggested, we do not see what useful service they could do the human body. It is quite ridiculous to suggest, as some do, that they serve as the breathing holes or the chimneys of the uterus, i.e. that through them the soot of the uterus blows out into the cavity of the abdomen, or that through them the fetus in the uterus breathes. It is to these parts that the placenta mainly adheres, shutting their apertures, while the fetus, being contained within its membranes from the end of the first part of the process of generation until birth, has no need to breathe at all during this time.
>
> Having duly weighed all these considerations, we judge the said Fallopian tubes in women and every kind of female animal are the real 'delivering vessels' or, if you prefer, the oviducts. It is through them that the eggs of the 'testicles' are transferred to the uterus.'

Conclusion

Reinier De Graaf was probably the first to comprehend and describe the true function of the Fallopian tubes. Moreover, he clearly recognized several pathological conditions. He described and illustrated the closed tube (hydrosalpinx) and understood the abnormality of that condition. He also described the development of tubal pregnancy, which was poorly understood or even unrecognized by his contemporaries.

Even today, many aspects of the transport of the fertilized egg through the Fallopian tube remain obscure. Modern scientists like Vizza *et al.* (1995), who studied three-dimensional organization of the smooth musculature in the Fallopian tube by scanning electron microscopy, and Paltieli *et al.* (1995), who studied real-time in-vivo ciliary activity in Fallopian tubes using a laser scattering instrument, are still looking for the same answers. De Graaf would have applauded these workers! The scientific methods used by De Graaf to achieve his goals are still an example for any modern scientist. De Graaf combined the findings from the dissecting table, animal experiments and clinical observations, and made a critical appraisal of the available literature. The insights thus achieved were a major contribution to the understanding of human procreation.

It is awkward that De Graaf's name will always be associated with the ovarian follicles, and not with the uterine tubes. De Graaf himself never claimed any priority for his description of the ovarian follicles at all, and wrote: 'Vesal, Fallopia, Vocher Coiter, du Laurens, de Castro, Riolan, Bartholin, Wharton, Dom. de Marchetti and others have described these vessicles under various names.' As illustrated here, De Graaf did claim priority where the correct anatomy and function of the uterine tubes were concerned. It would have been more appropriate if history had decided to speak of the Graafian tubes.

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