



## REVIEW ARTICLE

### HISTORICAL BACKGROUND OF ANOVULATORY INFERTILITY - UNANI PERSPECTIVE

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#### ABSTRACT

Ovulation is the central event in female production. Coordinated effects of hypothalamic gonadotropin releasing hormones, pituitary gonadotropins, ovarian estrogens and follicular response to these effects result in ovulation. Any derangement of the above factors results in ovarian dysfunction. In classical Unani literature, various physicians mentioned the detailed description of female genital organs. Soranus of Ephesus (98- 138 AD) father of gynaecology, gave a detailed description of ovaries noting their shape, size and position. He believed that conception was most likely to take place directly after menstruation. He mentioned that ovaries were attached to uterus and were not of firm consistency but glandular and covered with membrane. Aristotle (Arastu) and Galen (Jalinoos) mentioned that both male mani (sperm) and female mani (ovum) are responsible for conception. Galen (Jalinoos) states that if both baiza (ovaries) of any animal are either excised or crushed or make it colder with shokran, then conception will not take place. Therefore this paper has been entitled for historical review of anovulatory infertility in perspective to Unani medicine.

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## INTRODUCTION

The natural urge to procreate assured an interest in fertility and an admonition from the omnipotent to be 'fruitful and multiply' (genesis 1:28) added impetus to our mammalian instincts. So from the earliest times, it was apparent that the human race had an interest in beginning interrupting or discontinuing the reproductive process. All too soon however, some couples faced what the Talmud describes as "living death of bareness". The knowledge of anatomy and reproductive process dates back to the Stone Age people but the first detailed information comes from Egyptian papyri which describes many gynaecological complaints and recipes to increase fertility. Kahun papyrus (1850 B.C.) describes various methods used for the detection of fertility and 17 prescriptions for infertility. The Greater Berlin papyrus (Bruge Papyrus) describes infertility and mentioned prescription which consists of a mixture of fat, mandrake and sweet ale, boiled together and swallowed by woman to be taken every morning for four mornings after intercourse. Egyptians knew the existence of the ovaries, possibly from the rites preceding the embalming process and from vaginal examinations.<sup>1,2</sup>

The old Hebrew codes about the timing of sexual intercourse (mid cycle after 12 days of abstinence) to increase fertility. Bible confirms the interest of ancient Hebrews in the fertility process and they were aware that conception was possible seven days after the cessation of menses. Medicine paved its primary sources in Greece. It was Greeks who were aware of female reproductive organs. But the real change came with Hippocrates and his school. Born in 460 BC, Hippocrates wanted to break away from the way medicine of the time was practiced, which was closer to magic, and develop a system of medical reasoning based on rational thinking. Infertility was recognized as a medical problem which needed diagnosis and treatment and women were not subject to exclusion because of it.<sup>1</sup> Hippocrates was well aware of the problems of infertility and theorized a number of causes for it and had formulated numerous treatment options. "When a cervix is closed too tightly the inner orifice must be opened using a special mixture of red nitre, cumin, resin and honey. Or it could be dilated by inserting a hollow leaden probe into the uterus enabling emollient substances to be poured in". Despite these "advances", women in Greek times were considered as a "chastised male", an inferior creature. The uterus was considered an irrational soul and to be at the origin of all sorts of ills.<sup>1,2</sup> Hippocrates (460-377 B.C.) advocated a theory of pangenesis or preformation which states that semen were produced from both partners and contained elements from all parts of their bodies which flowed together forming a fruit and

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then developed into a baby. It was assumed that simultaneous orgasm must occur for conception to take place. Alternatively he advocated intercourse directly after menstruation to achieve a similar result.<sup>1,3,4</sup> Herophilus (IV Century BC) described ovaries and were called the female testicles/didymis (twins).<sup>1</sup> Aristotle (384-322 AD) was the first to record that intercourse was necessary for pregnancy to occur and he believed that semen and menstrual blood mixed in the uterus and formed a fetus. He developed various theories related to menstruation and infertility.<sup>1</sup> He made a comparative study of the uterus in various animals and studied the embryonic development of the chick and clearly stated the fundamental problem of sex, hereditary, etc.<sup>5</sup> He knew the function of the ovaries because he refers to the effect of castration on female animals.<sup>6</sup>

During the Roman era, the role of the gods was just as important as medicines. During the feast for Mars, the priests to this god would run through the city whipping the bellies of infertile women with a goatskin whip.<sup>2</sup> In Roman medicine, Soranus of Ephesus (AD 98- 138) gave the first scientific account of gynaecological anatomy and regarded as father of gynaecology gave a detailed description of ovaries noting their size, shape and position. He believed that conception was most likely to take place directly after menstruation. The period prior to menstruation was infertile because the uterus was "overloaded". He indicated that ovaries were attached to uterus and were not of firm consistency but glandular and covered with membrane.<sup>1</sup> Rufus of Ephesus in his book entitled "The names of the parts of the body" described the oviducts. Claudius Galenus (131-201 AD) taught that there was a mixing of male semen from the testes and female semen from the ovaries resulting in conception. He called the ovaries *the testes muliebris*.<sup>7</sup> Galen states that if both ovaries (*baiza*) of any animal are either excised or crushed or make it colder with *conium maculatum*, then conception will not take place.<sup>8</sup> There was little advancements in the treatment of infertility during Roman times.<sup>2</sup>

During the middle Ages, however, it was understood that procreation was a necessity and important to the "continuation of the species". It was not considered a reason for annulling a marriage. If a couple's sole reason for sexual intercourse was not for procreation, their fertility would be decreased. Infertility could also be the consequence of sins committed; infidelity, and blasphemy could also give rise to infertility. Fertility might be regained with prayer and fasting.<sup>2</sup> In middle ages; Rhazes has mentioned infertility and its causes and treatment in his book *al hawi*. He has mentioned whenever conception does not occur due to anovulation, obesity and hirsutism are the common findings. He has also mentioned the first line of treatment is to induce menstruation.<sup>9</sup> Rabban Tabari discussed about treatment of infertility and benefits of coitus, steps to be taken before and after coitus.<sup>10</sup> Holy Abbas has given a detailed description of anatomy, physiology, embryology and infertility and its causes. He states that Normal temperament of ovaries is hot and moist which is essential for it to carry out the basic function. An ovary produces a matter (follicle) which secretes (ovum *mani*). Ovaries utilises the blood supplied to them and causes complete metabolism, through its *hararat*, eventually the blood becomes white and viscous due to *lazoofat* and capable of producing an ovum in a similar manner as milk is formed in breast. *Ali Abbas* is also states that *quwah* controls the following functions:

- Male and female sexual powers and functions of copulation
- Fertilization of ovum
- Implantation of ovum

*Ali Abbas* has applied the four powers operating under *tabiat (quwa tabiyah)* viz *jazibah, masikah, mughayirah (hazima)* and *dafiah* in the formation of fetus.<sup>11</sup> Reproductive faculty (*Quwat tanasuliah*) is served by both *quwat ghaziyah* and *quwat namiyah*.<sup>12</sup> He defines infertility as inability of procreation either due to the defect in male or female or both. Cause of infertility due to the female partner can be due to defect in ovaries as a result of anovulation (*qiillat madda manwia*), accumulation of phlegm that must be excreted from the body in fallopian tube, or any obstruction either congenital or acquired in cervix.<sup>11</sup> Avicenna whose canon of medicine remains the encyclopedia for almost 700 years has given the anatomy and physiology of ovaries. He states that ovaries are the organs of reproduction<sup>13</sup> and the faculties responsible for the generation of sperm (male *mani*) and ovum (female *mani*); as well as for all sexual functions and formation of the fetus in the mother's womb are of two types:

- a) *Al quwa al muwallidah (generative faculty)*
- b) *Al quwa al musawirah (formative faculty)*

#### a) Al quwa al muwallidah (generative faculty)

*Alquwah al muwallidah* is that *quwa* which separates the essence of *mani* i.e. sperm or ovum, from *imshaj* (compounds) of the body inside the and ovary and makes each of its part to become a particular organ. *Ibn sina* is of the opinion that *quwate muwallidah* is of two kinds: one kind is that which generates *mani* (sperm and ovum) and the other one which gives different combinations to different potentialities of *mani* according to future organs. This *quwa* is also called as *quwah mughayirah ula* (primary transformative power) thus this *quwah* controls oogenesis and process of menstruation in females etc.<sup>3</sup>

#### b) Al quwa al musawirah (formative faculty)

*Quwah* is the property which gives shape to each part of *mani* (ovum) which is required by that particular species to which this *mani* (ovum) and any other shape close to that particular individual.<sup>14</sup> *Ibn sina* states that the formative faculty is that whereby delineation and configuration of the organs is produced with all their cavities, foramina, positions and relations to one another, their smoothness or roughness and so on – all being controlled up to the final limits of their natural dimensions.<sup>13</sup> Avicenna defined infertility as when conception fails to occur or when there is a difficulty in conception either due to the defect in male or female partner.<sup>13</sup> Defect in female partner are attributed to the diseases of *aaaze mani* (ovaries), *rehm* (uterus) or *nafsani* (psychological).<sup>13</sup> Ismail jurjani, in his book *zakhira khawarzam shahi*, described seven main etiological factors for infertility with sign, symptom and treatment and can occur due to both partners. One of these seven factors is the defect in ovulation which occurs due to abnormal temperament of ovaries.<sup>15</sup> Avenzoar (Ibn Zuhr) states that *Ovaries* are the organs essential for reproduction.<sup>16</sup> One of the eminent scholar of western caliphate during the middle ages was Averroes (Ibn Rushd) who was of the opinion that *rehm* performs two important functions i.e. it is for child birth and excretion of *khoon haiz*.<sup>8</sup>

### **Rehm consists of following four types of quwa(faculties):**

- i) *Quwwat hafiza*: protects the fetus and its weakness causes *uqr* or *usre hamal*.
- ii) *Quwwat masika*: retains the fetus within the *rehm* till *viladat* and its weakness leads to *isqaat*.
- iii) *Quwwat dafia'h*: expels out the fetus at parturition and its weakness causes *usre viladat* and increases the risk of *isqaat*.
- iv) *Quwwat jaziba* :absorbs the *nutfa* and its weakness causes *uqr* or *usre hamal* <sup>8</sup>.

The Renaissance marks the period of undeniable scientific progress and advancements in modern day thinking and treatment of infertility. Thanks to da Vince and others, the mysteries of the female body were gradually resolved and scientific thinking and reasoning replaced magic and the gods.<sup>2</sup> Lenardo da vinci (1452- 1519) was the first person to represent the structure of ovaries.<sup>1</sup> In 1562, Bartolomeo recommended that husbands should put their finger in the vagina after intercourse to encourage conception. This was the ancestor of the idea of artificial insemination.<sup>2</sup> Gian Matteo De Gradi of Milan (1524 -1531), Jan Swammerdam and Johann Van Horne (1666) mentioned that the mammalian female testicles, like the ovaries of birds, were the site of egg formation.<sup>1</sup> Andreas Vesalius (1514-1564), the “father of Modern Anatomy” was the first anatomist who described the ovary as containing sinuses (follicles) with watery fluid. <sup>1,17</sup> Gabrielle Falloppio (1523 – 1562) dissected the female testes and searched for the semen which he thought was stored in them.<sup>1,18</sup>

It was not until 1664 that stenson introduced the term ovaria <sup>1</sup>Regnier De Graaf (1672) refuted Aristotle's theories of fertilization, and <sup>2</sup>described ovaries and follicles but he assumed that entire follicle was ovum. Sperm was first identified under the microscope by von Leeuwenhoek in 1677.<sup>2</sup> Marcello Malpighi (1681), the pioneer microscopist introduced the term corpus luteum. William Hunter (1718-1783) described the corpus luteum. Percival pott (1775) and Karl Ludwig postulated that removal of ovaries in humans caused amenorrhoea.<sup>1</sup> In 1752, Smellie was the first to carry out experiments and describe the fertilization process. (Morice et al., 1995) John B. Davidge (1794) evolved the theory that the menstruation results from excitation of the uterus by the ovaries.<sup>1</sup> William Cumberland Crinkshank (1745-1800) noticed a yellowish white point in each ovarian follicle and opened one of the developed follicles to take up the minute object on the point of his knife. He placed it under the microscope it was found to be an ovule (ovum) and so clearly that a blind man could hardly deny it.<sup>1</sup> Despite the progress that was made during these times, infertility was almost synonymous with the female; and it was rare that the husband was considered as a cause. Even during this age of enlightenment, a real ambiguity existed. Women became the source of continual interest but were considered weak and sensitive and thus unfit to have anything to do with public and professional life; thus they were made to live indoors, to lead a dependent and subjugated life. Although progress was being made in the origins of infertility, because of a woman's apparent fragility, she automatically was at fault when the couple was infertile.<sup>2</sup> The nineteenth and twentieth century's were marked by tremendous advances in the diagnosis and treatment of infertility. <sup>2</sup>Prevost and Dumas (1824) detailed their observations of ovulation and formation of corpus luteum. Negrier (1840) and Rivelli (1893) demonstrated that a follicle ruptures each month and that ovulation does not

occur before the onset of menarche or after the menopause.<sup>16</sup> Polycystic ovaries were first described by J. Lisfranc in 1830. Pouchet (1847) described cyclical cervical mucus changes during the menstrual cycle and believed that it would be possible from these to predict ovulation. Edward F. W. Pflinger (1863) evolved his theory of menstruation. He believed that enlarge Graafian follicle sent nerve impulses to the spinal cord. In response there was a dilatation of uterine and ovarian blood vessels leading to thickening of endometrium and later menstruation. Hermann Fol (1877) was the first to observe fertilization, as it occurred in starfish. Edouard Van Beneden (1883) discovered that both ovum and sperm reduced their chromosome count by one half so that the fertilised ovum had a full complement of genetic material. Charles Edouard Brown Sequard (1890) claimed that an aqueous extract of ovarian tissue could have a rejuvenating effect on women. Louis Auguste Prenant (1898) suggested that corpus luteum was a gland of internal secretion. <sup>1</sup>After all, fertilization was described as the union of an egg and a sperm in 1898. <sup>2</sup>Josef Halban (1900) concluded that the ovary produced a substance which leads a specific influence on genital organs. Van De Velde (1905) first demonstrated the fact that body temperature shows a biphasic pattern during ovulatory cycles (with a difference of circa 0.5°C between the follicular and luteal phases).<sup>1</sup>

Rowe (1906) stated that ovulation occurred at the end of a period of quiescence and directly caused the period of hypertrophy which occurred prior to menstruation.<sup>1</sup> Adler (1907:1908) described the histological changes of endometrium throughout the menstrual cycle and Meyer (1911) and Rugae (1913) outlined the stages of development of the corpus luteum.<sup>1</sup> The general process of ovulation was detailed by Robinson (1918) and Allen et al (1930). The Graafian follicle was found to grow to size of about 15mm in diameter and gradually reach the surface of the ovary. The growth of the follicle accelerated prior to rupture but Hartman (1939) noted that the actual rupture of the follicle, which was aided by rise in intrafollicular pressure, was not an explosive process but a gradual opening. The ovum with its zona pellucida and attached follicular epithelial cells was then discharged (ovulation) into the peritoneal cavity to be caught by the fimbriae of the uterine tube.<sup>1</sup> Hartmann (1929) noted that the average size of human ovum varies from 0.133 to 1.140mm in diameter.<sup>1</sup> Allen and Doisy (1923) found that a hormone (estrogen) was present in liquor folliculi which was capable of inducing estrus in ovariectomized animals. George Corner and Williard Allen (1929) isolated progesterone. Irving Stein and Michael Leventhal (1935) described a series of infertile patients with amenorrhoea and polycystic ovaries whose menstruation returned following ovarian wedge resection. Brewer (1942) observed that the first signs of regression and degeneration of the corpus luteum, in a non pregnancy menstrual cycle, occurred about the 10<sup>th</sup> day of its existence. During the follicular phase of the menstrual cycle the waking temperature remained low. Viergiver and Pommerenke (1944) found that cervical mucus production increased in quantity throughout the follicular phase and reached a peak around the time of ovulation. Barton and Weisner (1945) showed that postovulatory progesterone was responsible for the raised temperature level, characteristic of the luteal phase of the cycle. Kistner and Smith carried out the first clinical trials of ovulation induction using a close structural analogue of clomiphene. Robert Greenblatt et al were the first to report successful induction of ovulation and pregnancy following

clomiphene therapy.<sup>1,18</sup> Gemzell et al (1952) announced the first successful induction of ovulation using human pituitary gonadotropins.<sup>1,18,19,20,21,22</sup> Lunenfeld et al. (1960) succeeded in extracting a potent gonadotropin material from the urine of menopausal women and showed that this preparation enabled the induction of ovulation and pregnancy in a large series of amenorrhoeic women.<sup>23</sup> 80 years after the description of fertilization, in 1978, the first "test-tube" baby was born in England and in 1981, her in-vitro sister was born. The first IVF baby born in the US was in 1981, pioneered by fertility specialists at Eastern Virginia Medical School in Norfolk, Virginia.

Since those early days, a little more than 25 years ago, tremendous progress has been made in the understanding, diagnosis and successful treatment of so many of the causes of infertility. And step by slow step, infertile women have come to be considered patients in her own right, instead of a curiosity and condemned member of the human society, living in silence and misunderstanding; no longer being considered witches and burned at the stake, but replaced as the center of medical and scientific attention, and possibly lying at the very source of all human survival.<sup>2</sup>

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