Recombinant Gonadotropins Used in Fertility Treatments [1]

By: Lane, Alison Keywords: egg maturation [2] fertility drugs [3] synthetic hormones [4]

First manufactured in 1988 by Serono laboratories, recombinant gonadotropins are synthetichormones [5] that can stimulate egg [6] production in women for use in fertility treatments. Recombinant gonadotropins are artificially created using recombinant DNA technology, a technology that joins together DNA from different organisms. In vertebrates, naturally-occurring gonadotropins regulate the growth and function of the gonads, known as testes [7] in males and ovaries in females. Medical professionals can derive female gonadotropins from the urine of pregnant and post-menopausal women, often using it to facilitate *in vitro* [8] fertilization [9], or IVF. With the rapid development of assisted reproductive technologies like IVF, demand for human-derived gonadotropins rose to a global yearly demand of 120 million liters of urine by the beginning of the twenty-first century, which resulted in a demand that could not be met by traditional technologies at that time. Therefore, researchers created recombinant gonadotropins to establish a safer and more consistent method of human gonadotropin [10] collection that met the high demand for its use in fertility treatments.

Within vertebrates, the endocrine system is responsible for creating naturally-occurring gonadotropins. Endocrine glands, such as the pancreas or the ovaries, secrete chemical messengers known as hormones [5] into the blood, where they flow throughout the body and influence cells that have a hormone's corresponding receptors. Two of the main gonadotropic hormones [5], luteinizing hormone [11], abbreviated LH, and follicle-stimulating hormone [12], abbreviated FSH, are produced by a pea-sized gland in the brain called the pituitary gland [13]. Gonadotropic hormones [5] regulate the primary reproductive organs, also known as gonads. Those organs are the ovaries in females and the testes [7] in males. On a monthly cycle for most females, the pituitary gland [13] naturally produces FSH and LH in order to stimulate the ovaries to produce a single matureegg [6].

The bodies of some women who experience problems with fertility may produce insufficient or abnormal amounts of gonadotropins like FSH and LH. In fertility treatments such as IVF, fertility specialists can administer injections of FSH and LH to stimulate women's ovaries to grow egg [6] follicles, or fluid-filled sacs containing immature eggs. For fertility treatments such as that, fertility specialists often proceed with administering an injection of human chorionic gonadotropin [14], shortened to hCG or HCG, in order to push those egg [6] follicles to maturity for collection and later for use in fertility treatment. Fertility specialists need to collect mature eggs from the woman's body for IVF because non-mature eggs are not capable of successfully producing an embryo upon insemination. As of 2020, hCG is colloquially known as the pregnancy [15] hormone [12] because it is produced by the placenta [16], an organ attached to the uterine lining that nourishes the growingfetus [17] and is used to detect pregnancy [15] in urine testing strips.

Modern research on gonadotropins dates back to the early twentieth century. Two researchers from Germany namedSelmar Aschheim [18] and Bernhard Zondek [19] found in 1927 that the blood and urine of a pregnant woman contains anegg [6]-maturing substance, which is modernly known as hCG. In 1929, two years after that initial discovery, Zondek hypothesized that the pituitary gland [13] produces two gonad-stimulating hormones [5], later named FSH and LH. Zondek's hypothesis was partially founded on his previous research where he implanted pituitary glands taken from cows and humans [20] into prepubescent animals, causing rapid onset of sexual development. Shortly thereafter, other researchers began to investigate whether gonadotropins derived from animals could benefit women who had clinically under-functioning ovaries.

Beginning in the 1930s, researchers investigated animal sources of gonadotropins intended for clinical use in infertile patients who cannot produce adequate amounts of gonadotropins. For many women with under-functioning ovaries, they can lose their ability to produce mature eggs, or ovulate, and therefore cannot become pregnant. Researchers investigated the use of pregnant horse [21] urine as one of the first animal-derived sources of gonadotropins. Pregnanthorse [21] serum gonadotropin [10], or PMSG, for example, was first described by researchers Henry Cole and George Hart from the University of California, Davis in Davis, California, in 1930. Commercially-produced PMSG was available on the market in 1938, but was later discontinued because women who took PMSG did not always develop mature eggs as a result of the treatment. In general, animal-derived gonadotropins for clinical usage were primarily discontinued in the 1950s due to the dangers of antibody formation, or a reaction of the immune system to what it perceives as foreign invaders. With the use of some animal-derived gonadotropins, women would experience severe allergic reactions. Others would often only result in a biological neutralization of the gonadotropin [10], meaning the woman's body nullified the hormone's effects. However, some animal gonadotropin [10] medications were still available in a few countries in Europe as late as 1998. Beginning around the 1950s, researchers shifted to collecting and purifying human gonadotropins directly from human sources, such as human urine and pituitary glands.

In the decades before 1995, scientists collected human gonadotropins from human urine and pituitary glands harvested from

deceased cadavers, the latter of which ultimately led to some serious adverse effects among those treated with those hormones [5]. Researchers linked the use of human pituitary gonadotropin [10] with a fatal degenerative brain disorder, Creutzfeldt–Jakob disease, decades after its introduction into human fertility treatments. Though researchers derived gonadotropins from both cadavers and human urine around the same time, ultimately, both sources had issues. While the administration of human pituitary gonadotropin [10] increased patients' risks for serious health outcomes, urine collection had issues associated with its collection capabilities.

In the 1960s when mass urine collection for fertility treatments began, there were only four urine collection centers, located in the Netherlands, Spain, Italy, and Israel. Around 600 women donated urine at the different collection centers. Altogether, they produced enough urine, around 120,000 liters over the span of a year, to satisfy the global demand for gonadotropins in the 1970s. However, due to the invention of new fertility treatments such as IVF, global demand quickly increased. By the beginning of the twenty-first century, the global yearly need was more than 120 million liters of urine to collect enough gonadotropins from human urine for use in fertility treatments. Critics of that approach began raising questions about the safety and procurement capacity around the 1970s. Aside from being a limited resource, many researchers claimed there was a lack of regulatory control and a risk of disease transmission caused by contamination between urine samples. To overcome the limitations of urine-derived human gonadotropins, recombinant gonadotropin [10] research began starting as early as 1975.

The research that ultimately led to the development of recombinant gonadotropins, which are created using recombinant DNA technology, began in 1975 shortly after the first creation of recombinant DNA molecules in 1972. Recombinant DNA is DNA that has been artificially created through the joining of DNA from different organisms. Generally-speaking, in that process, scientists add a gene of interest to a vector, usually in the form of a bacterial plasmid or virus, which then introduces it into a host cell where it integrates into the cell's DNA. Consequently, the host cell expresses the gene of interest as it grows and divides into new cells with the recombinant DNA. In 1975, researchers Premila Rathnam and Brij Saxena from Weill Medical College at Cornell University [22] in Ithaca, New York, uncovered a novel discovery into the protein building-block sequence of one of the primary gonadotropins, FSH. Background research continued until ten years later in 1985 when scientists cloned the FSH gene, meaning that researchers were able to make multiple copies of the gene for use in recombinant DNA technology. Ultimately, scientists created recombinant gonadotropin [10] preparations for FSH, LH, and hCG.

After scientists created recombinant gonadotropins, pharmaceutical company Serono began its commercial production in 1988. To produce recombinant gonadotropins, scientists selected Chinese hamster ovarian cells as the host cells, because of their efficient response to foreign DNA and their capacity to grow at a large enough scale for commercial production. Once Serono laboratories succeeded in creating the recombinant version of gonadotropin [10] for clinical usage in 1988, they later began licensing their technology to be marketed throughout the European Union in 1995. Additionally, other pharmaceutical companies began producing different types of recombinant gonadotropins around the same time. Beginning in the early 1990s, many IVF institutions began reporting pregnancies after prescribing recombinant gonadotropins to women for ovarian stimulation.

The research community tends to disagree on the fertility-related success of recombinant gonadotropins compared to urine-derived gonadotropins. In 2010, researchers from Europe named Philippe Lehert, Joan Schertz, and Diego Ezcurra conducted a meta-analysis involving 4040 participants. The meta-analysis directly compared the effectiveness of recombinant gonadotropins versus urine-derived gonadotropins, measuring effectiveness by the number of eggs collected and pregnancies established. The researchers found that although recombinant gonadotropins produced larger numbers of eggs, there was no statistical significance between the two methods in terms of rates of pregnancy [15]. That means that researchers could not confidently assert that the recombinant gonadotropins caused the production of the larger quantities of eggs.

As of 2020, scientists continue to study the effects of recombinant gonadotropins and its efficacy on fertility treatments. Researchers also use similar technologies to create synthetic hormones [5] that balance hormones [5] produced by other endocrine glands, such as the production of synthetic hormones [5] meant to balance the function of the thyroid. Additionally, scientists have used recombinant gonadotropins to study the implications of gonadotropins in the development and outcomes of certain types of cancers. For example, in a 2007 study, researchers found that women with breast cancer who were given recombinant hCG had a smaller rate of cancer growth over the span of two weeks than women who were given a placebo. Overall, recombinant gonadotropins are a way of meeting the increasing demand for hormones [5] for a variety of reasons, including disease modeling and fertility treatments.

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Subject

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