Insight into Sperm-less Conception of Virgin Mary from Reproductive Biology Perspective

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Abstract
How the Virgin Mary, a symbol of chastity and a lofty figure, conceived Jesus Christ has been a mystery since the beginning of the Christian era and will remain so. Just as we do not have a biological tissue sample belonging to Jesus Christ to subject to tests, we do not have any biological material which might identify the Virgin Mary as a mosaic, chimera or hermaphrodite. Although current scientific knowledge offers us the possibility that this pregnancy was an example of parthenogenesis (activation of an unfertilized female gamete to form a new individual animal or plant), the presence of the Y chromosome in Jesus complicates the matter. Thus, the present review aims to present data which to explain scientific alternatives as to how the Virgin Mary might have conceived Jesus Christ. We believe that the answer to this scientific problem may be of benefit in the treatment of infertile patients wishing to become pregnant.

Keywords: Virgin, Reproductive biology, Fertility

Introduction
The activation of an unfertilized female gamete to form a new individual in animals and plants is called parthenogenesis [1-3]. Parthenogenesis is a sexual, but unisexual, form of reproduction. It is not an asexual form of reproduction where somatic organs and cells are formed by cleavage or budding. Parthenogenetic reproduction requires the presence of a germ cell and its transformation to a zygote [4-7]. Almost all the offspring formed through this method are female and have the ability to continue their lineage on their own. Some of these species also have males, and when necessary the female can reproduce by mating with a male. Some species, however, have no males, and mating is not usual. These species can reproduce only by parthenogenesis. Parthenogenetic reproduction takes place in certain female plant species too [8]. This form of reproduction is not seen in male plants. In the latter, pollens are either degenerated or sterile [9].

The purest form of parthenogenesis is seen in daphnia which do not have males. Some species can use parthenogenesis both out of necessity and facultatively. Certain species like phylloxera do not mate during the summer; its females lay eggs, from which offspring are formed. However, the same phylloxera mate with males in autumn to produce stronger eggs for winter. Among the species which reproduce in this way, fertilized eggs produce female offspring, while the unfertilized eggs produce the male offspring. Among certain animals that reproduce parthenogenetically, heterosis, a form of reproduction through polyploid hybridization between taxonomically different species, is seen. In rudimentary or incomplete parthenogenesis, the zygote reaches only a certain stage in its embryological development. In complete parthenogenesis, however, fully developed female organisms are formed from unfertilized eggs. Parthenogenesis is a common form of reproduction in invertebrates like insects and arthropods. In vertebrates, parthenogenesis can be seen commonly in some fish species, amphibians, some birds, turkeys, and reptilians. Honeybees have the potential for parthenogenetic reproduction such
that the queen bee mates only once in its lifetime and stores sperms. After mating, the queen bee uses unfertilized eggs for five years to form male bees and fertilized eggs to form queen bees and female worker bees [1-9].

With the exception of certain shark species and the Komodo lizard, this form of reproduction without males is rare among higher species. Although rudimentary parthenogenesis can be seen in mammals, there has been no report of an instance of in-the-wild complete parthenogenesis. A number of experimental parthenogenesis models have been developed [10,11]. An interesting commonality seen in the experimental models is the activation and propagation of eggs secondary to physical stimulation such as being scratched or pierced with a needle. In fact, a complete, fully developed rabbit was produced through experimentally-induced parthenogenesis. No case reports of sperm-free reproduction in humans exist. Even though a case was published in 1995, this case was not accepted as an example of pure parthenogenetic reproduction [12]. Although cytoplasmic and nuclear modifications that take place during the fertilization of the oocyte by the sperm can be performed in the laboratory (Ca++ injection, electrical stimulation, certain chemicals, osmotic, etc.), the pregnancies did not continue due to various reasons, including insufficient and pathological placentation, and poor alveolar development after the embryos were transferred [1-3,5].

Gynogenesis and androgenesis are types of parthenogenetic reproduction which can take place between the members of the same or similar species. In this form of reproduction, the sperm penetrates the ovum, but syngamy does not occur (the nuclei do not merge) and there is no real fertilization. Still, the nuclei which did not merge produce female (gynogenetic) or male (androgenetic) embryos. In gynogenesis, the nucleus of the sperm degenerates before it unites with the nucleus of the oocyte, whereas in androgenesis, the nuclei of the oocytes degenerate. As a result, embryos contain only maternal or only paternal genomes. There are different mechanisms involved in the formation of mature embryos from oocytes not fertilized with sperms [8,9]. In certain living things, oocytes go through two consecutive meioses to reduce the number of chromosomes to half, and this event is called meiotic parthenogenesis. However, meiosis and halving of the number of chromosomes is not a must in all species (ameiotic or zygotic parthenogenesis). In other species, after the chromosome number is halved, the polar body is taken back in and a cell with a 2n structure, ready for syngamy, is formed (automixic parthenogenesis) [13].

Taxonomically different species can combine parthenogenesis and hybridization for polyploid reproduction. In the case of somatic/diploid or polyploid reproduction, cells have a diploid (2n) or polyploid (3n, 4n, 5n, etc.) number of chromosomes. Using a haploid number of chromosomes, male bees can have generative and haploid reproduction. Parthenogenetic reproduction can be induced in frogs, starfish, worms, and rabbits using certain chemicals like ionomycin as well as some alcohol derivatives used in culture media and intra-cytoplasmic calcium injections [14,15]. Parthenogenesis can be stimulated, though rarely, by leaving the oocytes in hypo- or hypertonic media, by hemolymph injection into the oocyte, by giving the oocyte a thermal shock, or by using media containing methanol and certain cations. Introducing HCG or gonadotropin into the culture medium can lead to the emergence of some morphological structures resembling a polar body [16]. Parthenotes formed as such are like pre-implantation embryos. However, all blastocyst-like structures found in cultures must not be interpreted as parthenotes. If drosophila oocytes are placed in a hypotonic medium, meiosis starts again and parthenogenetic reproduction occurs. When high potassium and polyethylene glycol is added to the media housing the oocytes and the pH value of the media is kept low, the resulting embryos have higher chances of being full-term and healthy [17]. Healthy and mature young frogs and rabbits have been produced through artificial parthenogenesis [18].

Similarly, when oocytes that discarded their polar bodies are exposed to an electric current at a certain voltage, the polar body is taken back into the cell, creating a state resembling a fertilized oocyte. For instance, if porcine oocytes are exposed to cytochalasin B, they expell the polar bodies at a rate of 25%. Electrical stimulation of these oocytes leads to the generation of tetraploid blastocysts. However, the majority of these cells degenerate before they complete the blastocyte phase [19]. Possible reasons for the loss of parthenogenetic embryos in early pregnancy include [20]:

- Impaired expression of imprinted genes,
- Inadequate placental development and spongiform trophoblastic placenta,
- Hypertrophy of extra-embryonic tissues,
- Lack of paternal genes,
- Retarded development, and
- Thick alveolar septum.

Is the Virgin Mary’s Pregnancy with Jesus a Case of Parthenogenetic Reproduction?

Virgin Mary conceived Jesus Christ as a virgin without having sexual intercourse with a male, and was still a virgin after delivery. This doctrine is known as the “immaculate conception” [21-24]. However, we do not have sufficient historical and scientific data about how she became impregnated. Some authors believe that her pregnancy was a result of parthenogenetic reproduction that is seen in certain insects, and animal and plant species, and that occurs without the involvement of sperms [25]. Although this form of reproduction that results from the spontaneous activation of the oocyte without a need for a male partner is common in lower organisms, it has not been reported in mammals, except in isolated cases [26]. However, mammalian oocytes can be activated through a mechanism similar to that of intra-cellular calcium oscillation which spermatogenesis causes at the fertilization stage in the in vitro medium and as such, a cleavage division can be triggered. The resulting parthenogenetic embryos that are born full-term and healthy can thrive in certain species, while they die at different stages of embryonic development in others. The arrested development or basic mechanism causing death is associated with genomic imprinting in which the expression of the genes belonging to the father is prevented in the embryo.

The elimination of the paternal genome leads to poor embryonic development, insufficient placentation, and a spongiform trophoblastic placenta, which in turn cause early loss of the fetus. A major requirement for a healthy parthenogenetic embryo is the ability of the oocyte to form a complete and functional centrosome in the absence of a sperm centriole. Throughout the stages in the process of embryonic development from cleavage to morula and blastocyst, and the resulting formation of germ layers and organs, the healthy occurrence of meiotic and mitotic, and then only mitotic division requires the generation of a functional centrosome. If the oocyte can generate a centrosome and perform imprinting on its own,
then all female individuals reproduced in these species will be healthy. However, the formation of a functional centrosome is not as important in mammals as it is in lower species [27]. When a female shark living in an aquarium in Nebraska got pregnant in 2007, the possibility of parthenogenetic reproduction in cartilaginous sharks and mammals was recognized. There were only female sharks in the aquarium, and no male sharks. Thus, mating was out of question. However, the female shark could have mated with a male shark before being brought to the aquarium, and stored its sperms. The ability of female sharks to store sperms and use them when necessary is a fact that has been known for a long time. Still, the female shark is known to have the ability to store sperms for up to six months, and this particular female shark had been brought to the aquarium several years before she became pregnant. Therefore, it was not possible for the shark to have mated and stored the sperms to get pregnant. The DNA analyses of the newborn shark did not reveal any paternal contribution, and the pup was found to have an exclusively maternal genome. In another study published before this one, the parthenote formed from two oocytes in mice was transplanted an IGF 2 gene, which fulfilled the function of the paternal genome, and by modifying epigenesis, healthy neonates were produced [28].

One Islamic reference to the Virgin Mary emphasizes that she did not grow up as other humans, but, being a special human being, was raised ‘like a flower’ [21]. Was this written to indicate that she, as opposed to other women, might have the ability to give birth to a child without needing a male? Actually, it may, because most flowers contain both pollen, each of which has multiple sperms and ovarian structures with one or more eggs. The sperm and egg in the same flower are fertilized to form new embryos. A similar form of reproduction is seen in hermaphrodite nematodes, called C. elegans [29-32]. There are also case reports of the co-presence of both the gonad and testis tissues in humans [33]. Of these cases, about 10% are formed by the combination of multiple zygotes; they are known as chimera whose karyotypes were found to be chi 46 XX/46, XY [34]. Rarely, embryos with only-female or only-male karyotypes may be formed [35,36]. Despite these facts neither chimeric nor hermaphrodite pregnancies in mammals have been reported yet.

If a living organism consists of cell populations with two or more genetically distinct structures, and if these cells are formed from different zygotes, these organisms are called chimeras, and the condition is known as chimerism. When cells with genetically distinct structures arise from a single zygote, rather than different zygotes, the organism is called a mosaic. Living things in the chimeric form may be generated by the fusion of two fertilized eggs or the fusion of early embryos. Similarly, an animal having more than two distinct blood types occurs more frequently than is commonly thought, and is seen because the healthy fetus carries the cells of its dead twin in its body. Chimerism can be hereditary or acquired, as when it develops secondary to the transfer of allogenic hematopoietic cells by bone marrow transplantation or transfusion. Chimerism may also occur due to vascular anastomoses in non-identical (fraternal) twins. There are reports, though not many, of chimerism in assisted reproductive technology cases [37]. Most chimera animals are fertile, and although sex determination based on the presence of testicular or ovarian tissue is attempted, there are also intersexual cases.

Although tissue with fetal DNA extends to the edge of the placenta, having a syncytial-capillary barrier, this structure originating from the chorion frondosum and decidua basalis does not usually allow mutual passage of cells. Certain fetuses can be interpreted as micro-chimeras due to maternal DNA that passes from the placental bed to their circulation. The opposite condition, where fetal DNA passes to the maternal circulation, can also be seen. The DNA that goes into circulation may, rather than staying in the circulation, settle in tissues like the heart or the brain [35,36]. Many neonates have a small amount of their mothers’ cells in their circulation or tissues. As the infant grows older, the number of these cells decreases. If the number of cells is not reduced, or a high number of maternal cells have passed to the infant, the risk for autoimmune diseases is markedly elevated. Most marmosets are cases of hematopoietic-chimerism that developed secondary to blood transfusion that occurred during chorion fusion [38].

Parthenogenetic embryos in mice die because genes belonging to the father have not been expressed or extra-embryonic tissues have not been formed. However, because chimeric-parthenogenetic normal and gynogenetic embryos have two different sets of cells and genes, they are viable. Although there have been attempts to eliminate the parthenogenetic cells in these cases, first from the trophoblast tissue and then from yolk-sac mesoderm and endoderm, the remaining cells contribute to the generation of the main body, in which the male pronucleus is settled and the actual embryo and its organs are formed [39]. XX/XY chimera cases have the male phenotype and XY cells are involved in spermatogenesis. The cells which could not be eliminated in the parthenogenetic chimera cells, on the other hand, contribute to the formation of testes. Consequently, the resulting germ cells contain only healthy cell sequences [40].

Chimeric-parthenogenesis, as seen in mice and leading to the generation of a healthy embryo, was reported in one case in humans. Therefore, chimeric-parthenogenesis can not only allow the birth of healthy and term human fetuses, but also help us explain the mechanisms by which humans are generated without paternal contribution. Examples of natural parthenogenetic development in humans can be seen in benign ovarian teratoma cases. These benign tumors develop as a result of the migration of gametogenic cells which completed their first meiosis to the ovary, rather than to the genital ridge. In 1995, a case report of total parthenogenesis identified through peripheral leukocyte genetic analysis was published in Nature’s Genetics [12]. In this individual, karyotype analyses using the peripheral blood, urine, and fibroblast cultures showed that the person had a 46, XY/46, XX mosaic genotype. However, the distribution of genotypical characteristics varied in each tissue. Detailed analyses (FISH, microsatellite genotyping) of the X chromosome revealed maternal isodisomy in 23 chromosome pairs, by which it was confirmed that all peripheral leukocytes were gynogenetic or parthenogenetic. Initially, the person could not be classified either as a mosaic nor a chimera. Each of the maternal alleles found in cells containing the XX or XY genotype in the case originated from a single oocyte. Although the person could be interpreted as being a mosaic on the basis of this finding, since it did not originate from a common zygote, the person was instead considered a chimera. In their experimental study, Maleszewski and Bielak attempted to explain the same patient using modeling [41]. According to their model, the oocyte was parthenogenetically activated during or after the ovulation phase and completed its second meiosis in the absence of a sperm. Later, the same parthenote was fertilized by a sperm. However, as the parthenogenetic embryo that the sperm penetrated had more than one maternal pronuclei with
which it could have syngamy, the male pronucleus was re-located into a blastomere and continued its development there. Parthenogenetic embryos in mice do not block entry of sperms until they are in the 8-cell phase, since they have not produce a plasma membrane yet [41,42]. However, the incoming sperm cannot form a pronucleus or is trapped in a blastomer. In the following phases of embryonic development, parthenogenetic blastomeres cannot perform cleavage, and diploidization results. However, the blastomere containing the male pronucleus completes its development. Although this model is correct on several notes, it cannot be scientifically applied to the Virgin Mary’s pregnancy, as it includes the fertilization of the parthenogenetic embryo by a sperm.

Discussion
Based on information in the holy books and historical sources, we can safely assume that Mary was a healthy woman [21-24]. However, we do not have any information about her fertility status or karyotype. Still, considering the information presented above, it is not unreasonable to assume that Mary could have been an example of hermaphroditism or chimerism resulting from the combination of two different zygotes. Unfortunately, there is no blood sample or other biological tissue belonging to the Virgin Mary which we can test to prove our proposition. Similarly, we do not have any tissues belonging to Jesus Christ. Several studies have examined blood samples on the cremenals allegedly belonging to Christ and kept in a Cathedral in Turin, Italy. C-14 analyses conducted to identify the age of the cremenals found that the cremenal dated back to 1260-1390 A.D., raising doubts about its true use by Jesus Christ. To explain this inconsistency, some have suggested that when the cremenals were exposed to fire, the high temperature increased the amount of carbon in the material, and that was why the test results show the cremenals to appear younger than expected [43-45]. Similarly, forensic analyses using multiplex nested PCR testing of biological materials (dried blood and bloody tears) on statues claimed to have belonged to Mary showed that the materials were from a female human being. However, it is not known for sure that these statues were owned by Mary, and the biological materials on them may have originated from others (the sculptor, those who worshipped the statue or anyone who might have touched it) [46].

Furthermore, if Mary had got pregnant through a meiotic or zygotic parthenogenesis in her XX oocytes, then the child she gave birth to, Jesus Christ, should have been a female. We know from historical sources and information in the holy books that Jesus Christ was born a boy [21-24]. However, since no mating allegedly occurred, the presence of a Y chromosome in Jesus Christ cannot be explained scientifically by parthenogenesis. Although Liza S. and colleagues had found both XX and XY genotypes in the parthenogenetic-chimera case they reported, it turned out that the Y chromosome had resulted from the fertilization of the parthenogenetic embryo by a sperm [12]. Still, it is not possible to talk about the presence of a sperm in Mary’s pregnancy. Nevertheless, it is possible that a sperm and the chain of reactions triggered by the sperm may not be necessary to generate a full-term embryo [47]. Using biotechnology and genetic engineering methods to modify the expression and imprinting levels of non-growing or immature oocyte genes, Kono and colleagues merged two oocytes and produced new mice with healthy genomes by this oocyte-to-oocyte interaction without using a sperm [48]. Although these mice were initially described as parthenogenetic embryos, currently they are more commonly defined as bi-maternal embryos. This result is based on the principle of the number of loci imprinted in male germ cells (three) being lower than maternal imprinted genes (seven). Of the oocytes used, one had a fully grown oocyte genome, whereas the other was a non-imprinted and non-growing oocyte – an oocyte that had not completed its genomic development. Thus, using serial nuclear transfer technology, three paternal genes (IGF-2 and Dlk/Gtl2) were placed into the nucleus of the non-growing oocyte. Newly produced oocytes now had a paternal genome, and surprisingly, they produced adult bi-maternal mice. Unlike parthenogenetic and gynogenetic embryos, these embryos came to possess paternal imprinted Peg1/Mest, Peg3, Impact, and Peg10 genes [49,50]. However, the embryos were lost on ED13.5 or ED19.5 days due to a thick alveolar septum and irregular and poorly organized alveolar structure [51]. The concerned study demonstrated clearly that imprinting was the main, and maybe the only, barrier to parthenogenesis in mammals, and RNA and proteins produced from the sperm might not be necessary to obtain a fully grown embryo [52,53].

“Genomic imprinting” in mammals is the major obstacle to parthenogenetic reproduction in mammalians [47], as two different sets of genes (male and female) are required for imprinting. Still, despite having a single maternal gene set, the female mammal oocyte, containing all genes relevant to embryo formation (7 distinct genes), can generate a full-term embryo. However, due to the placentation defect and the lack of gene exchange between homologous chromosomes, either pregnancy cannot reach full-term, or full-term cases vanish in the short run because of the genomic deficiency. These results support the active role of and requirement for the male genome in the utilization of maternal resources by the fetus and placentation.

Conclusion
Consequently, Mary’s conception without male involvement cannot be explained (for the time being) on the basis of definitive scientific data due to the following reasons:

- In Mary’s sperm-less conception, it is not possible for the embryo to go to full-term, and even if it does, to live for a long time, because of a lack of genomic imprinting.
- Presence of the female gene set only prevents healthy placentation and alveolar development. As Jesus Christ was born healthy and lived for a long period of time, it can be said that he overcame the epigenetic barrier and had healthy placentation; thus, he must have had healthy genes from both sexes. However, we cannot, at our current level of knowledge, explain where the paternal genes and Y chromosome came from.
- Since Jesus Christ was a male phenotype, the Y chromosome in Jesus Christ cannot be explained by parthenogenesis.
- We do not have any biological material to show that Mary was a mosaic, chimera, or hermaphroditic.
- Likewise, we do not have any biological tissue samples from Jesus Christ for testing purposes; dating of the holy cerement in Turin indicated that it was produced more than a thousand years after the time of Jesus Christ.

Results to be obtained from extensive scientific research about Mary’s pregnancy might prove useful in the treatment of many infertility patients.

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