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OPINION

Potential autofertility in true hermaphrodites

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ABSTRACT

This article examines the studies on the pregnancies of true hermaphrodites and self-fertilization in hermaphrodite mammals that have been published in the last 40 years. The number of hermaphrodite pregnants reported in the literature since 1975 was 14, the number of pregnancies was 26 and the number of healthy born babies was 20. All of the babies that were born were male. The pregnancy developed following gonadectomy in seven cases (nine pregnancies). In some cases, either gonadectomy was not performed at all or it was performed after pregnancy (eight cases, 17 pregnancies). The karyotype was 46,XX in four of these eight cases that became pregnant despite *in situ* ovotestis while it was 46,XX/46,XY in the other four cases (chimera). In the literature, pregnancy cases that developed through self-fertilization were not reported in humans. However, autofertilization was detected in mammalian hermaphrodites such as domestic rabbit. Furthermore, the ovarian tissues of true hermaphrodites were mainly functional and ovulatory. The testicular tissues were mainly immature. However, spermatogenesis was determined in some cases. In fact, both ovulation and spermatogenesis were detected in some cases. All of these findings show that true hermaphrodites with ovarian and testicular tissues are potentially autofertile.

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Introduction

True hermaphrodites (TH) are individuals that possess ovarian and testicular tissues (ovotestis) [1,2]. Gonads can be in the form of one ovary (O) and one testicle (T), or more frequently, one or two ovotestes (OT), and may be located bilaterally, unilaterally and laterally. Krob et al. [2] reported that this distribution is as follows in a series with 283 cases: bilateral (OT/OT: 32.6%), unilateral (OT/O: 36.7%, OT/T: 12.1%) and lateral (O/T: 18.6%) [2].

Genotypic heterogeneous is found in TH. The karyotype is 46,XX in 60–70.6% of the cases, mosaicism containing Y chromosome in 20.2–33% (46,XX/46,XY chimera) and 46,XY in 7% of the cases [1,2]. So, Chimera (mosaicism) is the karyotype with the second frequency determined in TH. Chimera is a fertilization error and results from the fusion of two different zygotes in a single embryo. In chimerism, two oocytes are fertilized by two spermatozoa, then fusion of the both embryos takes place. Thus, a single embryo occurs results from the fusion of two different zygotes [3].

Ovulation and spermatogenesis were determined in hermaphrodites with ovotestis, and the pregnancies and births were reported [2]. This brought into the agenda whether fatherless pregnancies can take place and the self-fertilization potential of hermaphrodites with ovotestis. Indeed, there are certain articles published on this subject [4–6].

Pregnancy and childbirth in TH

The number of hermaphrodite pregnants with ovotestis reported in the literature is 14 while the number of pregnancies in these cases is 26 [7–20]. In these pregnancies, there were one premature, one immature, one stillborn and one abortion performed due to unwanted pregnancy. One baby died 2 h after the birth. There was also an ongoing pregnancy during the publication of the relevant literature. All of the babies born apart from these were healthy. All of the babies (fetuses) whose gender was reported were male (Table 1).

The number of the cases that became pregnant despite *in situ* ovotestis was eight (Table 2). Seventeen spontaneous pregnancies developed in these cases. Four of these cases were the cases with bilateral ovotestis to which one-sided gonadectomy had been performed during the infantile period [15,17,18,20].

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Table 1. Pregnancies and births in TH.

Reference	Karyotype	PN	Ages at childbirth	Delivery	Infant	RN
Narita et al., 1975 [7]	46,XX	1	31	Caesarean	Male, healthy	7
Mayou et al., 1978 [8]	46,XX	1	18	Caesarean	Male, premature	8
Kim et al., 1979 [9]	46,XX	1	21	Vaginal	Male, died after 2 h	9
Tegenkamp et al., 1979 [10]	46,XX	1	33	Vaginal	Male, immature	10
Williamson et al., 1981 [11]	46,XX	1	18	Vaginal	Male, healthy	11
Tiltman et al., 1982 [12]	46,XX	9	27–41	Vaginal caesarean	Nine children, unknown sex	12
Minowada et al., 1984 [13]	46,XX	1	25	Vaginal	Male, healthy	13
Starceski et al., 1988 [14]	46,XX	1	23	Caesarean	Male, healthy	14
Talerman et al., 1990 [15]	46,XX/46,XY	1	29	Caesarean	Male, healthy	15
Pereira et al., 1991 [16]	46XX	4	–	Vaginal	Stillborn (6 months), unknown sex	16
			–	Vaginal	Male, healthy	
			–	Vaginal	Male, healthy	
			27	Pregnancy	During publishing	
Verp et al., 1992 [17]	46,XX/46,XY	1	29	Caesarean	Male, healthy	17
Tanaka et al., 2000 [18]	46,XX/46,XY	1		Vaginal	Male, healthy	18
Schoenhaus et al., 2008 [19]	46,XX/46/XY	2	22	Abortion	Male, abortus	19
			39	Vaginal	Male, healthy	
Schultz et al., 2009 [20]	46,XX	1	21	Vaginal	Male, healthy	20

PN: pregnancy number; RN: reference number.

Table 2. Pregnancies and births in TH with *in situ* ovotestis.

Reference	Mother's karyotype	Gonads (r/l)	Ages at gonadectomy	*In situ* gonads at pregnancy	Ages (at pregnancy)	PN	Birth	RF
Mayou et al., 1978 [8]	46,XX	OT/O	–	OT/O	18	1	1 C	8
Tegenkamp et al., 1979 [10]	46,XX	OT/O	38	OT/O	33	1	1 V	10
Tiltman et al., 1982 [12]	46,XX	O/OT	52	O/OT	27–41	9	9 V/C	12
Talerman et al., 1990 [15]	46,XX/46,XY	OT/OT	1	–/OT	29	1	1 C	15
Verp et al., 1992 [17]	46,XX/46,XY	OT/OT	1 (r)	–/OT	–	1	1 C	17
Tanaka et al., 2000 [18]	46,XX/46,XY	OT/OT	1 (r)	–/OT	–	1	1 V	18
Schoenhaus et al., 2008 [19]	46,XX/46/XY	O/OT	–	O/OT	22	1	Abortion	19
					39	1	1 C	
Schultz et al., 2009 [20]	46,XX	OT/OT	1 (l)	OT/–	21	1	1 V	20

O: over; T: testis; OT: ovotestis; V: vaginal; C: caesarean; PN: pregnancy number; RN: Reference number.

Gonadectomy was not performed in two cases, and was not performed before pregnancy in two cases (it was performed after the childbirth) [10,12].

The karyotype was 46,XX in four of these cases with *in situ* ovotestis during pregnancy, while it was 46,XX/46,XY in the other four cases (chimera).

Phenotype and ambiguous genitalia

The phenotypic structures of TH varied. There were cases with totally normal external genitalia as well as cases with ambiguous genitalia [2,16,21]. There were even cases the phenotype of which was female despite a karyotype of 46,XY and which did not have ambiguous genitalia, and cases the phenotype of which was male and which did not have ambiguous genitalia despite having a karyotype of 46,XX. A case was 4-years-old. The karyotype was normal, 46,XY (G and C-banding) and she has been reared as a female. There was normal external genitalia, bilateral fallopian tubes, a uterus, a vagina and bilateral streak gonads [16]. In another case was 4-years-old. The karyotype was 46,XX in blood lymphocytes (G and C-banding) and he has been reared as a male. There was normal male external genitalia with right cryptorchidism and absence of Mullerian tubules [16].

This was also valid for mosaic hermaphrodites, i.e. the phenotypic structures of 46,XX/46,XY chimeric hermaphrodites were also variable. In addition to chimeras with a totally normal (male or female) phenotype, there were also chimeras with ambiguous genitalia. The phenotypic spectrum of 46,XX/46,XY chimeric subjects was extremely variable. They were normal (male or female) or ambiguous [3,21].

There was only clitoris hypertrophy as the finding of ambiguous genitalia in all of the TH that became pregnant and gave birth [7–20].

Puberty, menarche, ovulation and spermatogenesis

The secondary sex characters were normal, puberty and menarche were at the expected ages (12–14 years) and menstrual cycles were regular in all of the hermaphrodites with ovotestis that became pregnant [7–20].

Ovarian tissues (including the ovarian parts of the ovotestis) of the TH were mostly well-developed and normal-looking. Ovarian tissues almost always contained primordial follicles before puberty. There were also findings such as corpora lutea and/or corpora albicantia showing the ovulation stages after puberty as well [2,22].

The testicular tissues of TH were mainly immature [1,2]. However, almost all of them had developed seminiferous tubules. Spermatogenesis was determined in some cases [22–24]. One of them was a chimera case with a male phenotype and a karyotype of 46,XX/46,XY; and there were histologically ovulation findings in the ovary taken from this case, the father of one child [22]. So, this case was a chimera with both spermatogenesis and ovulation.

While the ovarian compartment of an ovotestis shows evidence of ovulation at puberty in ~50% of cases, spermatogenesis has not been observed in the testicular portion of an ovotestis. Spermatogenesis was observed in only solitary testes found in true hermaphroditism [2,22–24].

Self-fertilization/autofertilization

There was no hermaphrodite case that was reported to have become pregnant through autofertilization among humans. However, there were autofertilization pregnancies reported among mammals. In 1990, Frankenhuis et al. [25] reported that a case of combined hermaphroditism and autofertilisation in a domestic rabbit. A true hermaphrodite rabbit which was housed in isolation, became pregnant and delivered seven healthy young of both sexes. It was kept in isolation and when autopsied was again pregnant and demonstrated two functional ovaries and two infertile testes. A chromosome preparation revealed a diploid number of autosomes and two sex chromosomes of uncertain configuration [25].

Potential autofertility

All these data show that hermaphrodites with ovotestis have pregnancy and childbirth potential. These include chimeric hermaphrodites that possess Y chromosome (mosaics). Chimeric cases that become pregnant spontaneously despite *in situ* ovotestis (ovarian and testicular tissues) are the evidence of that [15,17–19].

As ovulation and spermatogenesis are determined in TH with ovarian and testicular tissues, is it possible for pregnancy through self-fertilization to occur in these cases? There is no such case reported (in humans) in medical literature. However, autofertilization was reported in mammals. Thus, this (self-fertilization) may be possible in humans, too. At least we cannot say that it is impossible for sure. For both ovulation and spermatogenesis were determined in certain cases despite being rare, while spermatogenesis was determined in certain hermaphrodites [22–24]. So, while the ovarian tissues of TH are mainly functional (ovulatory), their testicular tissues may also have spermatogenetic potential. This shows that TH have the potential of pregnancy through self-fertilization. Indeed, it is always potentially possible that a sperm from functional testicular tissues inseminates an oocyte from functional ovarian tissues in the same abdomen through self-fertilization. At least, it cannot be said that such a scenario can never happen. Indeed, this subject was discussed in the context of the birth of Jesus, and certain authors explained the pregnancy of Mother Mary with the following scenario:

> She is a chimera of 46,XX/46,XY type resulting from the fusion of two zygotes of different sex types and she develops both ovarian and testicular tissues in her body. In another word, she develops from the fusion of dizygotic male and female twins and she had both reproductive cell types (oocytes and sperms) in her body. Since XX cells tend to gather on the left side while XY cells on the right, she develops an ovary on the left side with a patent oviduct and a testis on the right side located in an ovarian position with no duct. Her intact female reproductive tract on the left side indicates that anti-müllerian hormone secreted by the contralateral testis is not adequate to induce complete müllerian duct regression during development on the left. Müllerian duct regression on the right side is however mediated by the antimüllerian hormone derived from Sertoli cells in the ipsilateral testis and testosterone secreted from Leydig cells does not prevent the regression of the Wolffian duct due to a lack of response to it or inadequate hormone levels at the site. Therefore, neither an oviduct nor an epididymis and vas deferens is present next to the testis on the right side, and lumens of a well-developed rete testis have an open access to the abdominal cavity connecting the testicular tubules to the abdomen and allowing the sperms to be picked-up by the contralateral oviduct. Both gonads are functional and produce spermatozoa and oocyte respectively after puberty. At the time of ovulation, estrogens increase the motility of the oviduct on the left side which results in a negative pressure in the tube and oocyte and sperms are picked-up into the tube with the help of this vacuum effect, taking both gametes to the fertilization site in the oviduct. Since the sperm contains a Y chromosome, this fertilization gives rise to an XY male embryo [4].

Chimeric case pregnancies reported in the literature and that the babies born from these pregnancies are all males also support this scenario [15,17–19].

Yes, there has been no self-fertilization case (among human beings) reported in medical literature. However, that self-fertilization has been shown in mammals indicates that this is also possible among human beings [25]. At least, it cannot be said that such a possibility is impossible for sure. Thus, the birth of Jesus can be explained with the self-fertilization of chimeric Mother Mary.

Nevertheless, certain authors defended that the birth of Jesus cannot be explained with any biological mechanism. Benagiano and Dallapiccola [6] discussed the birth of Jesus on certain options such as parthenogenesis, induced stem cells and sex reversal, and concluded the following; "Our position is simple: we could not find any known natural or experimental biological mechanism capable of explaining the conception and birth of Christ; therefore, we consider pure speculation any biological debate on the subject". While Thomas [26] opposed this view by saying 'If not parthenogenesis why not "*in vivo* embryogenesis" with Mary as a birth mother' and tried to explain the birth of Jesus with the theory of '*in vitro* embryogenesis'. The authors qualified this hypothesis of Thomas [27] as "totally supernatural", and they also found this view to be against Catholic and Orthodox faith in "Mother Mary's being the real (biologic) mother of Jesus".

Parthenogenesis, which is expressed as "virgin birth" in Greek, is a natural form of asexual reproduction observed in plants, invertebrates, fish, amphibians and reptiles [28]. Certain authors defended that parthenogenetic reproduction may also be possible among humans, and new opportunities in infertility treatment can be obtained thanks to human oocytes that are parthenogenetically activated [29–32]. Parthenogenetic processes may open new horizons in the treatment of infertility. However, the birth of Jesus cannot be explained with parthenogenesis. Because, while parthenogenetic pregnancy product cannot be male [6,26], Jesus is male. Nevertheless, some said that Jesus is "phenotypically male, while genotypically female". For example, Kessel [33] defended that Jesus is actually female by saying, "Jesus was not only conceived as a female but remained chromosomally such throughout life. Through the natural process of sex reversal Jesus became male, not instead of female but as well as female, assuming the phenotype of a man while retaining the chromosomal badge of a woman. Thus, Jesus was born and lived as the androgynous Christ" [33].

As Benagiano and Dallapiccola [6] say, this hypothesis of Kessel about Jesus can be explained neither theologically nor biologically. However, the fatherless birth of Jesus can be explained. It is possible that Mother Mary became pregnant as a result of self-fertilization as a hermaphrodite with ovotestis carrying Y chromosome and gave birth to a healthy baby boy (Jesus) as a result of this pregnancy [4,5]. The following question may be asked: how can a sperm that is synthesized in testicular tissues of Mother Mary fertilize an oocyte in another area (the opposite ovary)?

There are four mechanisms that are navigating the sperms towards the oocyte. These are the vacuum effect created by the negative pressure occurring with the estrogen effect in the tubes of the ovulatory side, sperm rheotaxis, sperm chemotaxis and sperm thermotaxis mechanisms [4,5,34]. During ovulation, estrogens increase the motility of the uterine tubes which results in a negative pressure in the oviducts and this produces a vacuum effect [4,5]. A sperm in the abdomen may be caught with this vacuum effect in the tubes. The sperm may even fertilize an oocyte in an area far from itself by passing through the abdominal cavity, changing direction or exhibiting transperitoneal migration in this way, and create intrauterine pregnancy by being implanted in the zygote uterus that develops as a result of this fertilization [35,36]. For the sperm heads towards the oocyte through rheotactic, chemotactic and thermotaxtic navigations [34]. Rheotaxis is a major determinant of sperm guidance over long distances in the mammalian female reproductive tract. Sperm reorient in fluid flow to align against the flow direction and swim upstream [37]. Chemotaxis is the heading of the sperm against the gradient created by certain chemicals that are secreted by the oocyte (sperm are attracted by chemoattractants secreted by oocyte and its surrounding cumulus cells and swim against the chemical gradient [38]. Thermotaxis is the swimming of the sperm against the temperature gradient (sperm swim against temperature gradient in oviduct) [39]. Preovulatory follicles were 1–2 °C cooler than neighboring ovarian tissues in women [40]. The sperm navigate towards the ovalutary area as a result of this temperature gradient.

The pregnancy of the chimeric (46,XX/46,XY) Mother Mary can be explained by these mechanisms. That the baby born (Jesus) is male supports this hypothesis. For all fetuses in hermaphrodite pregnancies male [7–20]. Why? Certain opinions were put forth in this regard. One of them is the warm oocyte theory. The left ovary is warmer than the right ovary due to venous drainage, and the functional ovary is generally located on the left in hermaphrodites. The warm oocyte in the left ovary may be preferring the sperm carrying the Y chromosome [5]. However, the following opinion seems more reasonable in this respect. Embryos formed by oocytes fertilized by a sperm

carrying an X chromosome may not survive because of a genetic disorder involving either the sex chromosomes or the autosomes. For example, an abnormal maternal X chromosome with Y genes may not pair well with a normal paternal X chromosome at fertilization. The pairing of the abnormal X with the shorter Y chromosome during early embryogenesis may not be as much of a problem in this rare condition [20].

It is interesting that Qur'an, which reports that Mother Mary became pregnant through self-fertilization, implies that she had ovarian and testicular tissues. It gives certain clues about it. For example, the 21st and 66th surah of Qur'an have a verse (expression) such as follows; "Mary had protected her chastity (genitals). And we had blown our soul inside of her (genitals)" (Qur'an, The Prophets 21:91, The Prohibition 66:12). While the genital system of Mother Mary is referred to with female pronoun (ha) with the expression "feeha" in one of the verses containing these expressions (21/91), it is referred to with a male pronoun (hi) with the expression "feehi" in the other verse (66/12). So, both male and female pronouns were used for the genital system of Mother Mary (not for Mother Mary; for her genitalia). This points to the existence of both male (testicular) and female (ovarian) tissues in the genital system of Mother Mary. Furthermore, in another verse of Qur'an, it is expressed that Mother Mary was raised "as a beautiful plant" [The Family of Imran (3), verse 37]. Obviously, a significant part of the plants are hermaphrodites and are fertilized through self-fertilization [41]. Indeed, according to Qur'an, Mother Mary did not have sexual intercourse with anyone and became pregnant as a result of self-fertilization [Qur'an, Mary (19), verse 20–34]. According to these data of Qur'an, Mother Mary was a true hermaphrodite with ovarian and testicular tissues. However, she was a female hermaphrodite. For, she is always qualified as a sister/mother in Qur'an as in "Sister of Aaron" [(19):28], "Mother of Jesus" [The Believers (23):50] and "Daughter of Imran" [The Prohibition (66):12]. In another verse, she is qualified as a woman (chosen woman, superior woman), with the expressions "Mary! God chose you; created you immaculate and preferred you to all of the women in the world." [The Family of Imran (3):42]. Furthermore, Qur'an also reports that her phenotype is normal female. For when her mother Anne gave birth to her, she said "My God, I gave birth to a baby girl" (Qur'an, The Family of Imran, verse 36). So, according to Qur'an, it can be said that Mother Mary was a true hermaphrodite, who did not have ambiguous genitalia, with a normal female phenotype, became pregnant through self-fertilization, and gave birth to a healthy baby boy (Jesus).

Conclusion

That ovulation and spermatogenesis were shown in hermaphrodites with ovotestis explains that TH have the potential of self-fertilization. Considering the migration property of the sperm and/or oocyte, it can be said that TH are "potential autofertile". That self-fertilization was shown in mammals (rabbits) also supports this hypothesis. In case a hermaphrodite becomes pregnant through self-fertilization, it is possible that she maintains this pregnancy until the term and give birth to a healthy baby boy. For, the literature data clearly show that some hermaphrodites become pregnant and give birth to healthy baby boys. All fetuses in the pregnancy of TH are male, although the reason for this is not fully known.

Disclosure statement

The author report no conflicts of interest. The author alone is responsible for the content and writing of this article.

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