Chapter 4
Complete Moles and Parthenotes Are Not Organisms

Nicanor Pier Giorgio Austriaco, O.P.

Abstract The complete hydatidiform mole is an embryo-like entity that is generated by an abnormal fertilization event. In the past, noted moralists have argued that hydatidiform moles are not embryos since these so-called embryos are substantially defective from the outset. More recently, however, other bioethicists have suggested that the human mole *may once have been* a human embryo. In response, I argue that the ontological status of moles, parthenotes, and other embryo-like entities that develop into tumors will depend upon two distinctions, the distinction between an active and a passive potential and the distinction between a whole and a part. I propose that an embryo-like entity that has an active potential to become a tumor in the whole (such entities would include complete hydatidiform moles and parthenotes) is a non-embryo, while an entity that only has an active potential to become a tumor only in the part (such entities would include partial hydatidiform moles) is an embryo, albeit a disabled one.

Keywords Complete hydatidiform mole • Embryos • Non-embryos • Organism • Parthenotes

4.1 Introduction

The complete hydatidiform mole is an embryo-like entity that is generated by an abnormal fertilization event. In human beings, moles develop into a disorganized mass that can become a germ-line tumor. In the past, noted moralists have argued

This chapter includes updated arguments initially made in my earlier essay, "Are teratomas embryos or non-embryos?: a criterion for oocyte-assisted reprogramming," Natl Cathol Bioeth Q 5 (2005): 697–706.

N.P.G. Austriaco, O.P.
Department of Biology, Providence College, Providence, RI, USA
e-mail: naustria@providence.edu

A. Suarez and J. Huarte (eds.), *Is this Cell a Human Being?*,
DOI 10.1007/978-3-642-20772-3_4,

that hydatidiform moles are not embryos since these so-called embryos are substantially defective from the outset. [Germain Grisez writes: "Many biologists and physicians going by appearance have believed these tumors to be embryos whose development had gone astray. But authoritative and recent examination of the question has led to the conclusion that these growths are simply tumors – rather disorganized but somewhat differentiating bundles of material deriving from an individual's own body. Teratomas are not malformed embryos." See Grisez (1970, p. 28). Benedict Ashley, OP, and Albert S. Moraczewski, OP, agree with Grisez: "Bedate and Cefalo argue from existence of hydatidiform moles and teratomas that genetic individuation is not sufficient since these entities arise from zygotes. This argument, however, seems definitively refuted since it is now known that the so-called 'zygote' in question is radically defective from the outset." See Ashley and Moraczewski (1994).] More recently, however, other bioethicists have suggested that the human mole *may once have been* a human embryo. For instance, Pietro Ramellini has argued that an androgenetic complete mole (AnCHM) that arises from the fertilization of an enucleated egg with two sperm was once a human organism during a "premolar" stage (Ramellini 2006). So, are moles, parthenotes, and other teratoma-forming entities embryos or non-embryos?

In this paper, I argue that the ontological status of moles, parthenotes, and other embryo-like entities that develop into tumors will depend upon two distinctions: the distinction between an active and a passive potential and the distinction between a whole and a part. I propose that an embryo-like entity that has an active potential to become a tumor in the whole (such entities would include complete hydatidiform moles and parthenotes) is a non-embryo, while an entity that only has an active potential to become a tumor only in the part (such entities would include partial hydatidiform moles) is an embryo, albeit a disabled one. Finally, I suggest that an inner cell mass taken from an intact blastocyst is a non-organism that is not unlike an isolated cluster of pluripotent stem cells.

4.2 Hydatidiform Moles and Parthenotes: Biological Notes

There are two kinds of hydatidiform moles (for reviews, see Slim and Mehio 2007; Devriendt 2005). In a partial hydatidiform mole, two sperm fertilize a normal egg resulting in a conceptus with 69 chromosomes. The presence of three copies of each chromosome (triploidy) leads to death early in the pregnancy or, more rarely, in late-term loss of the abnormal fetus. Partial moles are characterized by disorganized placental and fetal growth. However, and this is important, the partial hydatidiform mole often presents itself as a tumor associated with a recognizable fetus.

In contrast, in a complete mole, either two sperm fertilize an enucleated egg (approximately 20% of complete moles) or a single sperm fertilizes an enucleated egg and then undergoes a duplication of its haploid genome (approximately 80% of complete moles). Thus, the product of conception has 46 chromosomes – the normal number – but all of them are derived from the father. The resulting mass

that arises is made up solely of tissue derived from one type of embryonic cell type, the trophectoderm, though there is a report that *early* complete moles have cells derived from the inner cell mass (Zaragoza et al. 1997). In other words, the developed tumor is made up of exclusively placental tissue and there is no fetal tissue present. Complete hydatidiform moles always develop into teratomas.

Finally, a parthenote is an egg that has been activated to begin to divide and to develop in the absence of sperm [for a review, see Rougier and Werb (2001)]. There are many experimental procedures, mechanical, electrical, and chemical, which can artificially activate the mammalian egg in this way. In vitro, activated human oocytes have been able to develop to the 5-day, 100-cell blastocyst stage in a manner apparently indistinguishable at the gross morphological level from the early development of normal human embryos (Rogers et al. 2004). In vivo, there is evidence that human parthenotes develop into ovarian tumors [Oliveira et al. (2004); also, see Lee et al. (1997).] These observations may not be contradictory since a report that studied the development of mouse parthenotes in vitro suggests that in this species, activated eggs develop to what appears to be a blastocyst stage before becoming tumors (Hirao and Eppig 1997).

4.3 Hydatidiform Moles: Philosophical Analysis

So, are hydatidiform moles and parthenotes disabled embryos or non-embryos? Are they organisms or non-organisms? First, there is good reason to think that a partial hydatidiform mole is an abnormal human embryo not unlike those children born with a triploid genome. [Though there are reports of children born with a triploid genome, they do not survive beyond 10.5 months. For one case study, see Sherard et al. (1986).]

To explain, with partial hydatidiform moles, the tumor is often associated with a grossly abnormal but recognizable human fetus. The presence of this fetus suggests that with a partial mole, the extra copy of each gene distorts the development of the embryo. One manifestation of this abnormality is the development of a tumor. Or to put it another way, with a partial mole, an already abnormal embryo develops cancer.

On the other hand, there is also good reason to think that a complete hydatidiform mole is not an embryo. In brief, a complete mole does not have a complete *functional* genome. Thus, it lacks molecules ab initio that radically changes its developmental trajectory. Instead of becoming an organized structure of differentiated cells and tissues, a complete mole develops into a germ-line tumor of one cell type of placental origin.

To explain, recall that the complete mole inherits all of its 46 chromosomes from the father. This is significant because in mammalian organisms, a small number of genes (nearly 200 human genes in a recent count or 1% of the human genome [for details, see the paper Luedi et al. (2007); in the mouse, two significant papers have identified over 300 genes that are imprinted in the brain: Gregg et al. (2010a, b)] are

inactive if they are inherited from a particular parent and not from the other. This is the phenomenon called genomic imprinting [for a review of genomic imprinting, see Kiefer (2007) and Wrzeska and Rejduch (2004)]. For example, the *IGF2* gene encoding insulin-like growth factor-2 is expressed if it is inherited from the father, but it is imprinted, i.e., rendered silent, if it is inherited from the mother [for details, see Chao and D'Amore (2008), Ohlsson (2004), also see Ohlsson et al. (1993)]. In contrast, the *IGF2R* gene encoding insulin-like growth factor-2 receptor is expressed if it is inherited from the mother, but it is imprinted if it is inherited from the father (Wutz et al. 1997). Thus, in effect, a complete mole lacks all the imprinted genes that are only active if they are inherited from the mother. Functionally, therefore, a complete mole has an incomplete genome. Significantly, there is evidence from mice that suggests that the imprinted genes that are nonfunctional in moles have an effect on the development of the whole embryo from the very beginning at the two-cell stage (Rappolee et al. 1992). The expression of imprinted genes has also been reported in human preimplantation embryos (Monk and Salpekar 2001; Salpekar et al. 2001). Thus, the complete mole is a living system that lacks molecules that are absolutely associated with a human embryo. [For a description of the systems perspective that is presupposed here, see Austriaco (2002, 2004).] Not surprisingly, because of the absence of these molecules that are only present when the genes that encode them are inherited from the mother, the complete hydatidiform mole cannot progress through the developmental stages associated with early human embryogenesis. Instead, it simply grows into a tumor often composed of only one or, at most, a few cell types of placental origin, though as we already noted above, there is a report that early complete moles have cells derived from the inner cell mass.

Together, the data suggest that the complete hydatidiform mole cannot be and is not any kind of unified organism ab initio. In other words, from the beginning, it is not an individual member of a particular biological species distinguished by a species-specific developmental trajectory that consists of the sequential and ordered appearance of differentiated cells and tissues. Therefore, it cannot be an organism. It is not an embryo.

Challenging this conclusion, Ramellini has suggested that as moles develop and become highly disorganized, they may pass through an initial stage of normality where they are normal or nearly normal human organisms that then become subject to disorganizing forces. More specifically, he suggests that a complete hydatidiform mole arises from a premolar entity that has organismic life. This premolar entity would be a normal human embryo that develops to the blastocyst stage. At this point, cells constituting the trophoblast of the blastocyst would initiate a molar transformation, killing the embryo.

To respond, we begin by noting that there is a distinction between an active and a passive potential. An active potential is actualized wholly from within. It is indicative of an entity's nature – its ontological status. For example, an acorn has an active potential to become an oak tree. In contrast, a passive potential is actualized from without. It requires the active causal intervention of an external agent in order to be

realized. Thus, an acorn only has a passive potential to become a crucifix because it would need the agency of a master craftsman in order to realize this end.

Given this distinction, the transformation of a premolar entity into a complete hydatidiform mole that becomes a tumor could potentially be described in three ways. First, we could say that the complete mole is a human organism that has an active potential to become a tumor. This would be incoherent. By nature, human embryos do not become tumors. Thus, they cannot have an active potential to become teratomas. Second, we could say that a complete mole could have been a human embryo that had a passive potential to become a tumor. By definition, however, a passive potential needs an external agent in order to be realized, and it is clear from his narrative that Ramellini is referring not to external but to internal disorganizing forces arising from non-expressed or inappropriately expressed genes. He writes: "The exact underlying mechanism [of the molar transformation] is still largely unknown, but both paternally and maternally imprinted genes are involved, with overexpression of certain paternal, and lack of expression of certain maternal genes." [Ramellini (2006); however, we should also acknowledge that there is evidence that normal mammalian embryos have a *passive* potential for teratoma formation. For example, if a normal mammalian embryo is transplanted under the kidney capsule of an athymic mouse, it can develop into a teratoma. Here, it is likely that the abnormal physiological environment of the kidney capsule kills the embryo by transforming it into a tumor. For technical details, see Anderson et al. (1996)]. Thus, and third, we have to say for Ramellini a complete mole is a human embryo where one part of the whole had an "active" potential to become a tumor. (Properly speaking, since active potentials are manifestations of substantial forms, which are principles of organization, there can be no active potential for tumor formation, a process that involves disorganization rather than organization. Therefore, it is more proper to say that a tumor arises in a human being because of defect in the *material cause* that affects a part of the human embryo. To put it another way, a tumor arises because the formal cause, the human soul, is unable to properly realize the potencies in part of the material cause. This defect leads to the abnormal actualization of hidden potencies in the material cause that manifest themselves as the disordered growth we call a tumor. For this clarification, I am indebted to Professor Michel Bastit of the University de Bourgogne in Dijon, France.) In the course of development, this part develops into the tumor that radically distorts the overall trajectory of the embryo of which it is a part, killing it.

Given this analysis, we can respond by asking the following question: In a complete hydatidiform mole, do the genetic defects that distort its developmental trajectory leading to tumor formation affect the whole mole or only a part of it? If the imprinting or silencing defects affect the whole, then tumor formation is the actualization of an "active" potential that reflects the nature of the mole. (Again, properly speaking, there can be no active potential for tumor formation, a process that involves disorganization rather than organization. In this case, it is more correct to say that a tumor arises because of a defect in the *material cause* that affects the entire cell mass. To put it another way, a tumor arises because the formal cause, the human soul, is unable to properly inform the defective matter. This failure of

ensoulment leads to the abnormal actualization of hidden potencies in the material cause that manifest themselves as the disordered growth we call a tumor.) On the other hand, if the imprinting defects affect a part of the mole, then tumor formation is simply the distortion of a once normal embryo. Though to the best of my knowledge no scientific experiments on human embryos have been performed to directly address this question – incidentally, experiments that would be morally reprehensible – there is scientific evidence from developing mice that suggests that the absence of parentally imprinted genes impacts the development of the whole embryo and not only a part, even at the two-cell stage [Rappolee et al. (1992), also see the paper by Walsh et al. (1994)]. This suggests that tumor formation is a manifestation of the nature of the complete mole. Therefore, a complete mole is not an organism because an organism does not become a tumor. In contrast, as already noted above, the evidence from partial moles suggests that tumor formation is a manifestation of a defect in a part where one part of the embryo becomes a tumor in the context of the abnormal development of the fetus. Thus, a partial mole is an embryo, albeit a disabled one.

Finally, a comment: Based on the published report that identified cells derived from the inner cell mass in early complete hydatidiform moles, some bioethicists assumed that a complete hydatidiform mole undergoes normal human development to the blastocyst stage. At this point, the trophoblast would overwhelm and destroy the adjacent inner cell mass. There is no direct empirical evidence for this. In fact, a recent report describing the case of a complete hydatidiform mole, a placenta, and a coexisting fetus derived from a single in vitro fertilized oocyte challenges this assumption (Hsu et al. 2008). In this case, the complete mole and the intact fetus developed from a single 12-celled embryo. Though the exact mechanism behind this case of a complete mole/placenta/fetus combination is unclear, what is clear is that the cells that gave rise to the complete mole coexisted with the cells that gave rise to the intact embryo at the beginning of the pregnancy and that they developed into a tumor without overwhelming and killing the embryo proper. This would not be expected if the assumption that a molar trophoblast would have killed an adjacent embryo had been true. Therefore, I favor an alternative explanation for the presence of ICM-derived tissue in early complete moles: A complete hydatidiform mole is able to generate tissues of different cell types in a disorganized fashion early in its development.

4.4 Parthenotes: Philosophical Analysis

At this point, it is important to note the parallels between complete hydatidiform moles and parthenotes. Recall that a complete mole is an embryo-like entity that results from an abnormal fertilization event where two sperm fertilize an enucleated egg. Thus, a complete mole has the normal number of 46 human chromosomes, but they are all derived from the father. In contrast, a human parthenote results from an abnormal “fertilization” event where an egg has been activated to begin dividing.

In the process of activation, the haploid egg duplicates its 23 chromosomes. Thus, the parthenote too has the normal number of 46 human chromosomes, but here, they are all derived from the mother. Not surprisingly, therefore, mammalian parthenotes, such as complete moles, have a defective genome. In this case, they lack all the imprinted genes that are only active if they are inherited from the father. Not surprisingly, therefore, our analysis of the ontological status of parthenotes parallels our earlier analysis of the ontological status of complete hydatidiform moles.

For our analysis, the definitive question that arises is the following: Does the absence of the maternally imprinted gene products that are only produced when genes are inherited from the father impact the system dynamics of the whole parthenote ab initio substantially changing it so that the parthenote becomes a tumor, or does their absence only lead to a defective part of an embryo that becomes a tumor eventually killing the whole?

In response, we return to the key study, already mentioned above, that has shown that the absence of both paternally and maternally imprinted genes impacts the development of the embryo from the very beginning at the two-cell stage (Rappolee et al (1992). Moreover, the absence of the maternally imprinted molecules impacts that parthenote at the level of the whole since the scientific evidence suggests that the imprinted genes regulate the overall number of cells that develop in the blastocyst. In addition, another study has demonstrated that the organization of a parthenote differs from the organization of a normal embryo from the very start: In normal development, when the single-celled mouse zygote divides into two cells, these two cells, called blastomeres, are already not identical. One of the two cells divides ahead of its sister and tends to contribute most of its cellular descendents to the ICM that generates the embryo proper, which will develop into the baby's body, whereas the other, later dividing cell, contributes cells predominantly to the extra-embryonic tissue including the placenta, which will develop into the afterbirth [for details, see Piotrowska et al. (2001).] However, in contrast, when a single-celled mouse parthenote divides into two cells, these two cells do not behave in the way that normal blastomeres would behave [for details, see Piotrowska et al. (2001).] The first cell that divides does not necessarily contribute its descendents to the ICM. This is a small but significant difference in organization that points to the difference between the parthenote and the normal embryo at the very earliest stages of the development. In sum, all of these data suggest that the forces that lead to tumor formation are already present at the earliest stages of embryonic development. In other words, the system dynamics of the parthenote as a whole already differs from the system dynamics of the normal embryo since normal embryos do not become teratomas. Like the complete mole, a parthenote is not an embryo.

But what about blastocyst formation? As we noted above, there is evidence that human parthenotes have been able to develop to the blastocyst stage in vitro. If the parthenote is not an embryo, why does it develop at least until the blastocyst stage? There is a ready explanation for the development of blastocyst structures in the parthenote. Numerous studies have shown that the egg contains molecules from the mother that can compensate for defects in the embryo's genome. For instance,

embryos lacking the gene for E-cadherin, an essential molecule that glues cells together, are able to maintain their integrity until the blastocyst stage because the mother provides it with her E-cadherin. However, when the store of maternally derived E-cadherin is depleted, the embryo's cells dissociate and the embryo collapses (Larue et al. 1994). This defect is evident at the molecular level from the very beginning as levels of maternally derived E-cadherin molecules gradually decrease, but the morphological effects take time to manifest themselves. In the same way, it is not surprising that the absence of the maternally imprinted molecules in the parthenote does not completely manifest itself until the blastocyst stage. The molecular defect within the parthenote is temporarily masked by the molecules inherited from the mother. This, however, does not detract from the reality that the parthenote, in itself, is a teratoma-forming entity, a non-embryo, from the very beginning that has an active potency to become a tumor.

4.5 Conclusion

Finally, I would like to close with a brief word about the isolated inner cell mass. The earliest sign of cell differentiation during human development occurs during the transformation of the morula to the blastocyst with the appearance of the trophoblast and inner cell mass (ICM). The trophoblast gives rise to the embryonic contribution to the placenta, while the inner cell mass generates the embryo's body proper and its extraembryonic tissues [Gardner and Beddington (1988); also see the molecular analysis by Adjaye et al. (2005).] Is the ICM an organism or a non-organism? It is clear that an isolated ICM cannot continue developing into a mature organism. When placed in culture, these ICM cells eventually die, though some of them will be transformed into pluripotent ES cells via a still uncharacterized stochastic mechanism [for a representative paper, see Lerou et al. 2008.] Thus, I propose that the ICM is a non-organism that is not unlike a clump of pluripotent stem cells. ICM cells retain the ability to generate all the cell types and tissues of the mature organism, but they are unable to do so in an ordered and sequential way, the way that characterizes a *bona fide* organism, the totipotent embryo.

References

Adjaye J, Huntriss J, Herwig R, BenKahla A, Brink TC, Wierling C, Hultschig C, Groth D, Yaspo ML, Picton HM, Gosden RG, Lehrach H (2005) Primary differentiation in the human blastocyst: comparative molecular protraits of inner cell mass and trophectoderm cells. Stem Cells 23:1514–1525

Anderson GB, BonDurant RH, Goff L, Groff J, Moyer AL (1996) Development of bovine and porcine embryonic teratomas in athymic mice. Anim Reprod Sci 45:231–240

Ashley B, Moraczewski AS (1994) Is the biological subject of human rights present from conception? In: Cataldo PJ, Moraczewski AS (eds) The fetal tissue issue. The Pope John XXIII Center, Braintree, MA, pp 33–59

Austriaco N (2002) On static eggs and dynamic embryos: a systems perspective. Natl Cathol Bioeth Q 2:659–683

Austriaco N (2004) Immediate hominization from the systems perspective. Natl Cathol Bioeth Q 4:719–738

Austriaco N (2005) Are teratomas embryos or non-embryos?: a criterion for oocyte-assisted reprogramming. Natl Cathol Bioeth Q 5:697–706

Chao C, D'Amore PA (2008) IGF2: epigenetic regulation and role in development and disease. Cytokine Growth Factor Rev 19:111–120

Devriendt K (2005) Hydatidiform mole and triploidy: the role of genomic imprinting in placental development. Hum Reprod 11:137–142

Gardner RL, Beddington RS (1988) Multi-lineage stem cells in the mammalian embryo. J Cell Sci Suppl 10:11–27

Gregg C, Zhang J, Butler JE, Haig D, Dulac C (2010a) Sex-specific parent-of-origin allelic expression in the mouse brain. Science 329:682–685

Gregg C, Zhang J, Weissbourd B, Luo S, Schroth GP, Haig D, Dulac C (2010b) High-resolution analysis of parent-of-origin allelic expression in the mouse brain. Science 329:643–648

Grisez G (1970) Abortion: the myths, the realities, and the arguments. Corpus Books, New York

Hirao Y, Eppig JJ (1997) Parthenogenetic development of Mos-deficient mouse oocytes. Mol Reprod Dev 48:391–396

Hsu CC, Lee IW, Su MT, Lin YC, Hsieh C, Chen PY, Tsai HW, Kuo PL (2008) Triple genetic identities for the complete hydatidiform mole, placenta and co-existing fetus after transfer of a single *in vitro* fertilized oocyte: Case report and possible mechanisms. Hum Reprod 23:2686–2691

Kiefer JC (2007) Epigenetics in development. Dev Dyn 236:1144–1156

Larue L, Ohsugi M, Hirchenhain J, Kemler R (1994) E-cadherin null mutant embryos fail to form a trophectoderm epithelium. Proc Natl Acad Sci USA 19:8263–8267

Lee GH, Bugni JM, Obata M, Nishimori H, Ogawa K, Drinkwater NR (1997) Genetic dissection of susceptibility to murine ovarian teratomas that originate from parthenogenetic oocytes. Cancer Res 57:590–593

Lerou PH, Yabuuchi A, Huo H, Takeuchi A, Shea J, Cimini T, Ince TA, Ginsburg E, Racowsky C, Daley GQ (2008) Human embryonic stem cell derivation from poor-quality embryos. Nat Biotechnol 26:212–214

Luedi PP, Dietrich FS, Weidman JR, Bosko JM, Jirtle RL, Hartemink AJ (2007) Computational and experimental identification of novel human imprinted genes. Genome Res 17:1723–1730

Monk M, Salpekar A (2001) Expression of imprinted genes in human preimplantation development. Mol Cell Endocrinol 183:S35–S40

Ohlsson R (2004) Loss of IGF2 imprinting: mechanisms and consequences. Novartis Found Symp 262:108–21

Ohlsson R, Nyström A, Pfeifer-Ohlsson S, Töhönen V, Hedborg F, Schofield P, Flam F, Ekström TJ (1993) IGF2 is parentally imprinted during human embryogenesis and the Beckwith-Wiedemann syndrome. Nat Genet 4:94–97

Oliveira FG, Dozortsev D, Diamond MP, Fracasso A, Abdelmassih S, Abdelmassih V, Gonçalves SP, Abdelmassih R, Nagy ZP (2004) Evidence of parthenogenetic origin of ovarian teratoma: case report. Hum Reprod 19:1867–70

Piotrowska K, Wianny F, Pedersen RA, Zernicka-Goetz M (2001) Blastomeres arising from the first cleavage division have distinguishable fates in normal mouse development. Development 128:739–748

Ramellini P (2006) Life and organisms. Libreria Editrice Vaticana, Vatican City

Rappolee DA, Sturm KS, Behrendtsen O, Schultz GA, Pedersen RA, Werb Z (1992) Insulin-like growth factor II acts through an endogenous growth pathway regulated by imprinting in early mouse embryos. Genes Dev 6:939–952

Rogers NT, Hobson E, Pickering S, Lai FA, Braude P, Swann K (2004) Phospholipase C-zeta causes Ca^{2+} oscillations and parthenogenetic activation of human oocytes. Reproduction 128:697–702

Rougier N, Werb Z (2001) Minireview: parthenogenesis in mammals. Mol Reprod Dev 59: 468–474

Salpekar A, Huntriss J, Bolton V, Monk M (2001) The use of amplified cDNA to investigate the expression of seven imprinted genes in human oocytes and preimplantation embryos. Mol Hum Reprod 7:839–844

Sherard J, Bean C, Bove B, DelDuca V Jr, Esterly KL, Karcsh HJ, Munshi G, Reamer JF, Suazo G, Wilmoth D, Dahlke MB, Weiss C, Borgaonkar DS (1986) Long survival in a 69, XXY triploid male. Am J Med Genet 25:307–312

Slim R, Mehio A (2007) The genetics of hydatidiform moles: new lights on an ancient disease. Clin Genet 71:25–34

Walsh C, Glaser A, Fundele R, Ferguson-Smith A, Barton S, Surani MA, Ohlsson R (1994) The non-viability of uniparental mouse conceptuses correlates with the loss of the products of imprinted genes. Mech Dev 46:55–62

Wrzeska M, Rejduch R (2004) Genomic imprinting in mammals. J Appl Genet 45:427–33

Wutz A, Smrzka OW, Schweifer N, Schellander K, Wagner EF, Barlow DP (1997) Imprinted expression of the Igf2r gene depends on an intronic CpG island. Nature 389:745–749

Zaragoza MV, Keep D, Genest DR, Hassold T, Redline RW (1997) Early complete hydatidiform moles contain inner cell mass derivatives. Am J Med Genet 70:273–277