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Paper

Contrasting selected reproductive challenges of today with those of antiquity—the past is prologue

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ABSTRACT

Viewing human history through a medical lens provides a renewed appreciation for today's vexing reproductive challenges, as some modern dilemmas are actually continuations of similar challenges experienced long ago. Certainly there are many examples of assisted fertility therapy that were entirely theoretical only a generation ago, but have become commonplace in modern practice and society. In particular posthumous birth and infertility have, over time, been the focus of compelling social interest, occasionally even impacting national security and dynastic succession. While the concepts have remained static, the tools available to extend and improve reproductive success have changed radically. Appropriately regarded as confidential and private, an individual's reproductive details are typically impervious to formal study. Yet, archival sources including ancient literature and formal court records can occasionally provide evidence of otherwise deeply personal concerns of a different era. Our assessment finds the issues, worries, and desires of patients of antiquity to align closely with contemporary reproductive challenges. Because children and family have always been central to the human experience, the consequences of reproduction (or the lack thereof) can make substantial imprints upon the cultural, economic, and political landscape—irrespective of civilization or century. In this article, selected motifs are described in a broad historical context to illustrate how challenges of human reproduction have remained essentially unchanged, despite a vast accumulation of knowledge made possible by gains in reproductive science and technology.

Plus ça change, plus c'est la même chose.
-Jean-Baptiste Alphonse Karr (1808-1890)

INTRODUCTION

Whether experienced by commoner or king, the social value of a birth is difficult to overstate in the human experience. Just as in modern times, our ancestors occasionally found the process of pregnancy and birth difficult, and required some "special ministrations and relief". For this, it was quite logical to seek the assistance of some trusted and learned person; this report originates from the records of such transactions. Especially when considering the contemporary terms "posthumous birth," "posthumous conception" or "infertility", numerous instances from the past show that while the nomenclature may change, the basic circumstances remain fairly constant. Although it would be impossible to catalog every instance where legend or history supplies an antecedent for common reproductive dilemmas, the current report does sample some representative cases from antiquity to illustrate familiar themes. Recognizing that social and legal processes are still evolving to deal with these issues is also important. While applications of technology in the realm of modern medical science trace an impressive arc forward, a thoughtful look backward reveals a well-worn path of struggle where surprisingly little has changed over the centuries.

POSTHUMOUS BIRTH

Historical variations

The circumstance of posthumous delivery describes an unusual, although not particularly recent, development where a birth occurs after the death of a parent. Basic reproductive physiology causes the deceased parent more often to be the father, while death of the mother during childbirth is less common. The latter is sometimes (albeit incorrectly) exemplified by the birth of Roman Emperor Julius Caesar (100 B.C.-44 B.C.). This error probably developed due to the assumption that the abdominal delivery method in widespread use today was named for Caesar himself, who must have been

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born – if we trust folklore - via this namesake route. Yet, a more probable origin of the term Cesarean delivery derives from the verb *caedere* (to cut), particularly considering that babies delivered in this way were sometimes referred to as caesones in classical times. This emphasis on "cutting from the womb" is probably based on a legal requirement for any child of a Roman mother who died in childbirth to be removed from her womb. Such a posthumous birth would also be in technical fulfillment of prevailing religious beliefs, which proscribed burial of any woman who was still pregnant at death[1].

This situation was not particularly rare during the Roman era, considering how unsafe birth procedures then were. Pliny the Elder (A.D. 23-79) makes reference to a distant relative of Julius Caesar as having been born in this fashion: ab utero *caeso*, cut from the womb. However, it seems implausible for Julius Caesar himself to have been delivered by the operation which carries his name, as his mother could not have survived the procedure[2]. Classical scholars agree that she did survive; the voluminous correspondence that Julius maintained with his mother, Aurelia Cotta (120 B.C.-54 B.C.), throughout the son's reign provide ample evidence that this dangerous delivery method was not used[3]. It should be noted that, even much later in history, Robert II of Scotland (1316-1390) was a posthumous birth, delivered via cesarean and his mother Marjorie Bruce died shortly afterward[2]. Indeed, the modern operation commonly known as the "Caesarean section" was not successfully performed on a living patient until A.D. 1500[4].

A more accurate, and certainly more dramatic, example of posthumous (paternal) birth is found from the period of the 9th King of the Persian Empire, Shapur II (A.D. 309-379). When the father, King Hormizd II, was killed in 309, it was thought necessary to reserve the throne for his unborn child who was carried by one of the wives. To secure this succession, a remarkable *in utero* coronation occurred—with the Imperial Crown of Persia being placed directly upon the mother's pregnant belly[5]. Thus, when Shapur was eventually delivered, he was already king (his mother and others carried out government duties during Shapur II's antenatal life). Even more significantly from this same geographic area, the Prophet Muhammad (c.570-632) was born some six months after his own father died. This was why he was raised by an uncle (Abu Talib ibn 'Abd al-Muttalib, 549-619), who would prove to be an essential supporter of Muhammad during Islam's early formative period[6].

Later in the 14th Century, a pregnant widow survived Louis X of France, thus providing a European example of posthumous birth. His heir, John I (aptly named John the Posthumous) lived as King of France for less than one week (in November 1316) and provided western civilization with one of its shortest undisputed reigns[7]. Across the channel, England would see a posthumous birth of its own (with much greater dynastic impact) as the Tudor era began with Henry VII (1457-1509). He was delivered two months after his father died. Another famous Englishman born premature but still three months after his father died was Isaac Newton (1642-1727), whose massive contributions to science and mathematics were not presaged by his tiny dimensions at birth—the widowed mother noted that baby Isaac could have "fit in a quart mug"[8]. Less than ten years after Newton's birth, another fatherless baby who would later become England's King William III was born in The Hague. William (1650-1702) was delivered just eight days after his father succumbed to smallpox, and would eventually figure prominently in the decline of Cromwell's Commonwealth as England proclaimed its Glorious Revolution in 1688[9].

The seventh, nineteenth, and forty-second U.S. Presidents were/are posthumous births (Andrew Jackson, Rutherford B. Hayes, and Bill Clinton, respectively), as was John F. Kennedy's assassin Lee Harvey Oswald. In 1918, Taisia Solzhenitsyn became pregnant near Kislovodsk, but shortly thereafter her husband was killed in a tragic hunting accident. The son and future Nobel laureate Alexander (1918-2008) later described his earliest, turbulent memories forming against the background of Russia's civil war, settling finally into beautiful Cavendish, Vermont, but without a father.

Modern challenges and new directions

Posthumous births, while still rare, have certainly been facilitated by procedures (including the ability to cryopreserve and bank reproductive tissue) which have gained in sophistication, have become easier to access, and have increased in reliability. Advancements in assisted fertility treatments now enable human embryos to be frozen and stored for many years, possibly long after both genetic parents have died. This unfortunate situation occurred for the first time in 1983, when Elsa and Mario Rios of Los Angeles died in an aviation accident. The couple left behind two frozen embryos with no instructions on disposition at an IVF clinic in Melbourne, Australia. There was much speculation on whether the embryos had any lawful claim to the Rios estate, estimated at more than $1M[10]. Although a government commission in Australia recommended that the "orphan" embryos should be destroyed, the ultimate fate of the two embryos was never disclosed. Clearly, if such embryos remained viable after thaw and successfully implanted following transfer, any subsequent delivery would have resulted in a totally parentless posthumous birth. The maximum interval for storing a cryopreserved human embryo is unknown, although delivery of healthy twins following the transfer of embryos which had been frozen for 12 years has been reported[11].

Posthumous births may also occur when sperm is obtained from deceased individuals[12]. The first successful retrieval of sperm from a cadaver was reported more than 30 years ago, in a case involving a comatose man who sustained a traumatic brain injury from an automobile accident but whose family nevertheless requested sperm preservation[13]. The first successful conception using sperm retrieved post-mortem was reported in 1998, leading to a successful birth the following year[14]. Reproductive urologists typically advise surgical

extraction of sperm should occur within 24 hours of death, although motile sperm have been successfully obtained as late as 36 hours later[15]. As case reports accumulated describing techniques for posthumous sperm retrieval, it became clear that this reproductive technology was outpacing ethical or legislative control to direct its proper usage[14]. Ethicists correctly noted that developing fluency in a technical or scientific skill alone does not necessarily justify the endeavor[16]. One center in New York (Weill-Cornell College of Medicine, USA) responded to this by proposing their own institutional rules for post-mortem sperm retrieval (PMSR). Thus, the "Schlegel Criteria" were developed to address this procreative procedure: 1) there must be evidence of intended paternity for the deceased man, 2) next of kin/legal must provide consent (i.e., only the wife could provide consent for PMSR), 3) the man's death was sudden (permitting time-critical retrieval <24h post-mortem) and 4) the partner must consent to a 1-year waiting period to use the sperm therapeutically, for bereavement and assessment of recipient. The Cornell group published their findings concerning how PMSR was applied over an eight year interval, using these criteria to guide clinical practice[17]. Of the 22 families requesting this procedure, 18 were not candidates for PMSR based on the Schlegel Criteria. Four men (ages 29-36yrs) underwent PMSR after being declared dead but who were maintained on ventilator support (2 cases), or within the first 24 hours after death (2 cases). The average number of sperm vials cryopreserved per patient was three, sperm concentration was 17.6M/ml, and motility was 8.7%. All specimens were viable and demonstrated acceptable post-thaw motility[17]. Similar results have been reported from other institutions, and PMSR appears to be possible regardless of the cause of death or method of surgical sperm extraction. PMSR has a high success rate, with sperm retrieved in nearly 100% of cases, and motile sperm in 80–90%. After sperm have been obtained by PMSR, fertilization is generally achieved through intracytoplasmic sperm injection (ICSI) and in vitro fertilization (IVF). The pregnancy success rate with IVF is mainly impacted on the age of the female, and remains unchanged irrespective of whether the sperm was retrieved from a living or dead donor.

In America, the subjects of sperm use, posthumous birth, and inheritance of property were confronted by the U.S. Supreme Court in *Astrue v. Capato*. This decision was handed down in the October 2011 term, and involved a case where twins were conceived 18 months after the death of their father. The dispute centered on whether or not the twins were eligible to receive Social Security survivorship benefits. The mother conceived the children through IVF using sperm her husband had had frozen and stored before he died from cancer. When the twins were born, Ms. Capato applied for Social Security survivor's benefits for them. Her application was denied, and this action was affirmed by the U.S. District Court of New Jersey. Both Courts found that under federal law, the twins would qualify for benefits only if they could inherit from their late father in accordance with the intestacy law (regarding inheritance without a will) of Florida, the state where Robert Capato was domiciled at the time of his death. On appeal, the 3rd Circuit decided differently, finding that the undisputed biological children of an insured and his widow do qualify for survivor's benefits irrespective of state intestacy law. However, in a unanimous decision the U.S. Supreme Court reversed the 3rd Circuit ruling, appearing to settle some of the questions of posthumous birth in the United States in favor of the posthumously born to inherit estates and benefits on a late parent's demise[18].

The Astrue case underscores relevance of posthumous birth in today's society, and the ability to harvest and bank reproductive tissue makes it almost certain that further controversy and disputes will occur. At present, several hundred thousand cryopreserved human embryos are believed to be maintained in liquid nitrogen storage in the United States[19], and the United Kingdom has a supply at least as large[20]. An unknown but far greater number of sperm samples (and more recently, unfertilized oocytes) have been placed into cryostorage which could also be used for an expanding array of assisted fertility treatments. It will be important for reproductive specialists, legal experts, and bioethicists to work together and offer leadership as any future legislation addressing this issue is contemplated.

INFERTILITY

Historical variations

Careful examination of court medical records over the centuries reveals how successful reproduction (or the lack of it) has made deep imprints upon the cultural, economic, and political fabric of humankind. So fundamental has the concept of reproduction remained throughout human existence[21], all major belief systems seem to reserve special provisions for it. For example, Hinduism successfully absorbed an already extant fertility cult as Shiva was worshipped as a god of reproduction. In contrast, Buddhism gained early momentum from an ascetic rebellion proscribing all earthly entanglements, including family and offspring. Judaic precepts rallied against local fertility gods while Christianity sought to overcome what was perceived as licentious Greek and Roman fertility rites. Islam started as a reform movement, attempting to curtail the culturally accepted practice of polygamy[22].

The Biblical account of Genesis 30:1 describes Rachel, who cries out in anguish to Jacob "Give me children, or else I die". Ancient Hebrew manuscripts also tell the story of Elkanah, whose favorite wife Hannah was "barren". Peninnah, the other wife, taunted Hannah because of her infertility. Hannah prayed desperately for a son, and promised to dedicate him to the Lord's work. The prayer was answered with the birth of Samuel—the greatest, wisest, and last Judge of Israel[23]. Such stories resonated with common families, who understood the natural desire to have their progeny remain strong, safe, and productive. Unfortunately, the historical source material needed to document those struggles among typical families

of those times is virtually nonexistent today.

One notable instance where infertility afflicted a somewhat obscure man but nevertheless had tremendous repercussions for all of western civilization came from a disjointed scatter-plot of land within the Holy Roman Empire. In lands roughly corresponding to today's German state of North Rhine-Westphalia and the present-day Dutch province of Gelderland, a very serious problem developed when John William, Duke of Jülich-Cleves-Berg (1562-1609) died childless at age 46. Although his territorial holdings were tiny by continental standards, these duchies held vast wealth. Moreover, international attention was focused on the region due to its strategic location on the border with the fractured Netherlands. Although John was married twice, he was never able to produce a successor. This caused foreign powers to panic and their armies marched into Julich-Kleve on two occasions, first in 1609-10 and again in 1614. Remarkably, war fought specifically over the contested duchies was avoided, causing some historians to regard the Julich-Kleve succession crisis as the first time international diplomacy resolved a conflict. By 1618, the wider disputes of the times between Protestants and Catholics sadly escalated, culminating in the Thirty Years' War[24].

The reproductive scheming of Mary I of England (1516-1558) provides perhaps the most desperate ruse ever to overcome infertility. Mary actually staged two hoax pregnancies, the first beginning in September 1554 when she said her menses stopped, she gained some weight, and felt sick in the mornings. Mary's retinue of physicians, many close associates, and virtually the entire English Court were not inclined to challenge this evidence of pregnancy[25]. Recognizing the risks attendant to childbirth at the time, and trying to plan ahead in case of an obstetric disaster, Parliament set other business aside and passed an Act making Mary's husband Philip regent in the event of the Queen's death during delivery[26]. So it was with a mixture of high anticipation and great confusion that conflicting rumors spread throughout London about a birth, or, maybe there was no birth. No one was quite sure. Queen Mary continued to exhibit signs of pregnancy until July 1555, when her abdomen shrank: there was no baby. Interestingly, Mary announced that she was pregnant again two years later, and this time calculated that her baby would be due sometime in March 1558[27]. No heir was ever delivered then either, and Mary at last accepted that her half-sister would be her rightful successor (Elizabeth I, 1533-1603). Interestingly, when not preoccupied with imaginary pregnancies, Mary was able to introduce a new, stronger monetary system that would be used in England until the 18th century, create new trade routes with Russian, African, and Baltic markets, and revise the English tariff system[28]. But these accomplishments were not enough to overcome her lasting reputation as a religious tyrant, "Bloody Mary". Issues concerning English succession (including marriage and the succession rights of women) dominated her childless reign, and Elizabeth I (also childless), marked the last of the Tudor line.

The House of Stuart followed, where the disastrous obstetrical history of Queen Anne of England (1665-1714) stands in gloomy notoriety. At the time, the royal womb was monitored much like a national weather forecast. Her 17th and final recorded pregnancy ended on 25th January 1700, with the delivery of a male stillbirth. It is believed that Anne had either miscarried or given birth to stillborn offspring at least a dozen times. Of her five livebirths, all but one died before age two[29]. Anne's reign is regarded as politically successful; her support of Marlborough decisively crushed French power and forever altered European history. But her fertility problems, as history would have it, cleared the way for the House of Hanover to make its indelible mark on Europe, and eventually, in the American colonies.

Other empires, too, felt the sting of infertility. After achieving its hard-fought independence from the Ottoman Empire (1831-32), Greece finally got its own king—who by strange quirk of history happened to be named Otto (1815-1867). As Greece healed from its revolution, the public craved stability and hoped that Otto's marriage in 1836 would result in an heir to solidify the new Greek dynasty[30]. Unfortunately, this couple's infertility added greatly to their unpopularity and was a key reason for their subsequent overthrow in 1862. Otto was promptly replaced by George I of Greece who provided a relatively stable hand during his nearly 50-year reign[31]. Yet infertility also overshadowed George's own eligibility for this role: George's father was designated heir presumptive to the childless King Frederick VII of Denmark (1808-1863). This allowed a sister to become Queen Consort to Edward VII of England and thus mother to the famous George V; and for himself, to father 8 children including Andrew, the father of the current Prince Philip, Duke of Edinburgh. So once again, a royal crown took a circuitous route to compensate for the manifestations of infertility.

England faced yet another succession problem when William IV (1765-1837) died at age 71 with no legitimate heir, so a collateral relative was called to ascend the throne. This young niece, later Queen Victoria (1819-1901), is now believed to have carried a *de novo* recessive mutation for Hemophilia B. Due to William IV's failure to supply a suitable direct successor, this sex-linked disorder appears to have been introduced by two of Victoria's five daughters (Beatrice and Alice) into the ruling families of Germany, Spain, and Russia. However, because the present royal family of England descends from Edward VII (Queen Victoria's first son, 1841-1910) who was not affected, the Mountbatten-Windsor lineage has been free from Hemophilia B—unless the recently delivered Duchess of Cambridge (b. 1982) happens to be a carrier.

MODERN CHALLENGES AND NEW DIRECTIONS

For anyone—past or present—who wants to have children, infertility can be a devastating diagnosis. The psychological distress, anxiety, depression, embarrassment, and low self-esteem associated with infertility are known to affect both men and women in equal measures[32,33]. In many cultures,

the social stigma of infertility greatly magnifies its physical impact. Sociologists have shown how infertility can lead to divorce, loss of economic resources, and even cancelation of cemetery plots for burial[34]. A current and comprehensive understanding of infertility is not always easy, because the terms of "sterility", "infecundity", "childlessness", and "subfertility" are often used interchangeably. This inconsistency is partly due to the range of scholarship focusing on infertility. The disparity is likely greatest between demographic and clinical experts. Specifically, studies of infertility in a clinical context are focused on early detection and prompt treatment in individual patients. In contrast, demographers are more interested in measuring the impact of infertility at the level of entire populations, relying on census data and household surveys rather than information from clinic encounters[35,36]. Observations made over many decades have shown that the single most important factor influencing reproductive outcome is maternal age, which is closely associated with "ovarian reserve" (the natural oocyte endowment), a number females have at birth.

Experience accumulated from IVF has demonstrated that this fertility potential appears to decline first after the age of 30, moves downward rapidly thereafter, and essentially reaches zero by the mid-40s[37]. Conceptions after this age are exceedingly rare, unless oocytes obtained from a younger donor are used[38]. How best to estimate ovarian reserve is the subject of much debate. Passive assessments of ovarian reserve include measurement of serum follicle stimulating hormone (FSH), oestradiol (E(2)), anti-Müllerian hormone (AMH), and inhibin-B. Ultrasound determination of antral follicle count (AFC), ovarian vascularity and ovarian volume also can have a role. The clomiphene citrate challenge test (CCCT), exogenous FSH ovarian reserve test (EFORT), and GnRH-agonist stimulation test (GAST) are provocative methods that have been used to assess ovarian reserve[37]. While pregnancy rates after IVF are certainly impacted by non-ovarian factors including laboratory conditions, semen parameters, psychological stress and technique of embryo transfer, predicting response to gonadotropin treatment nevertheless remains an important aim in the evaluation of the couple struggling with infertility[36,37].

Medical treatment of infertility generally involves the use of fertility medication, medical devices, surgery, or a combination of these interventions – none of which were available even a century ago. In the present day, if conservative medical treatments fail to achieve a full term pregnancy, IVF may be considered. This technique generally involves the above-described stimulating of the ovaries with hormones to increase oocyte recruitment. After stimulation, the eggs are surgically removed from the ovary and fertilized with sperm under direct observation in the IVF laboratory. The resulting embryo is placed inside the woman's uterus under sonographic guidance, in a procedure known as embryo transfer. Since this treatment sequence places human embryos briefly in an exterior setting, they can be tested to determine which embryos have the best chance of survival and implanting once inside the womb. These assessments are collectively known as preimplantation genetic diagnosis (PGD).

The last decades have indeed reached an exciting time for reproductive research. In 2001, control of cellular senescence was discussed as a function of proper and safe reconfiguration of the predetermined number of divisions permitted during every cell's natural life-cycle, the so-called Hayflick Limit[38]. If the oocyte's ''expiration date'' could be successfully re-set, then this would represent perhaps the most significant breakthrough in the history of modern reproductive medicine. Fundamental precepts of reproductive biology are being questioned as new information becomes available, including the belief that females lose the capacity for germ-cell regeneration. For example, novel hypotheses for oocyte generation derived from ovarian surface epithelium (OSE) or hematopoietic progenitor cells are currently being explored. These potentially path-breaking investigations are based on the observation that while primordial germ cells in embryonal ovaries are of extra-ovarian origin, those generated during the fetal period (and postnatally) come from bipotent OSE mesenchymal cells. It has been reported[39] that human OSE stem cells could, under specified conditions, become distinct cell types including de novo oocytes. Additionally, continuous replenishment of the oocyte pool in the postnatal mammalian ovary has been proposed as evidence that oogenesis can proceed into adulthood[40]. These findings remain controversial[41] and await validation from other laboratories. Indeed, some scientists have been unable to demonstrate that progenitor cells of extra-ovarian origin actually can repopulate the adult ovary[42]. While their results supported the conventional view that a limited number of oocytes is formed before birth and deteriorates with age, the theory is still being tested. And finally, the basic paradigm of inevitable oocyte exhaustion which has been observed in every adult primate research animal ever studied, curiously, does not seem to apply to more ancient species. Specifically, while reptiles typically demonstrate a peak in mating and offspring production, their reproductive senescence has never actually been determined and suggests the potential for oocyte replacement into advanced age. The related ability to continuously replace teeth well into adulthood, for example, is another unusual regenerative capacity commonly seen in reptiles[43]—yet this is absent in virtually all mammals. Humans typically produce singleton offspring and sometimes twins but very rarely triplets and higher order multiple births, at least in the absence of embryo manipulation. In contrast, armadillo spp. include placental mammals which routinely produce genetically identical (clonal) offspring. What genetic differences might have triggered these differences in reproductive strategies? Did evolutionary pressure induce mammals to exchange a capacity for oocyte renewal for some more-favored survival trait? Did it happen by accident considering our survival past forty is, from an evolutionary perspective, a relatively recent development? While further discoveries in the areas of comparative biology

and reproductive genetics promise to provide clarification on these issues, equally daunting questions will no doubt come forward to replace them.

CONCLUSION

Posthumous birth and involuntary childlessness existed long before modern assisted reproductive technologies, and certainly were familiar concepts even before the terms were ever coined. As described here, careful reflection on times past can identify some of the same reproductive challenges that exist today[44]. At the highest levels of state function and political security, succession crises were an inherent feature of national systems, which led to complex rules of inheritance to preserve dynastic patrimony and government stability. Assuming human reproduction function was unimpaired, this system did usually help ensure an orderly transfer of power from one generation to the next. However, infertility was commonplace in times past as it remains today. Yet any mother or father still wants the very best opportunities for their offspring to thrive, and to offer their own wisdom and/or genes to the generations ahead. That formal adoption continues to offer an important and cherished opportunity to fulfill biological (albeit not genetic) parenthood and to transmit social traits illustrates a time-honored response to the scourge of infertility. Although impressive clinical techniques can offer much to alleviate the burdens of infertility in contemporary use, the ailment being corrected holds an ancient pedigree. The cultural memory of humankind carries many stories that portray, often between the lines, reproductive circumstances that have shaped our history as much as history has shaped ourselves.

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