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Short Communication

Thermoregulation of human embryos and hatchlings in a prenidial incubator using infrared microthermography

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ABSTRACT

A new trend in reproductive biology is to research advancements in medical care for the preimplantation patient on the basis of new technologies. Based on the size parameters of the preimplantation patient, the technologies of interest fall predominately under the head of integrated microfabrication technologies (IMT). Such technologies are able to produce integrated electrical, mechanical, and chemical systems and devices at the submillimeter, micrometer (micron), and nanometer scale. A few examples of IMT technologies include micro-electro-mechanical systems (MEMS), complementary metal oxide semiconductor (CMOS) technology, and nanotechnology. By employing microfabrication technologies in combination with large-scale technologies, the medicine-of-the-future will be able to care for the preimplantation patient in a sophisticated micro-milieu. A tragic fault of in vitro fertilization programs today is that most practitioners rely unimaginatively on crude laboratory dish methods suitable only for primitive biological specimens. Consequently, morbidity and mortality rates are extremely high in these programs. Of particular concern is that programs based on a crude laboratory paradigm do not account for the actual body temperature of the preimplantation patient. For this reason, such programs do not offer accurate thermoregulation of the body temperature. However, accurate thermoregulation forms the basis of a competent incubator system. To provide accurate thermoregulation, an advanced incubator care system is needed which uses the techniques of infrared microthermography to monitor body temperature. On this basis a new breed of incubator is emerging for the preimplantation patient—known as the prenidial ("pre-NID-e-al") incubator, a word derived from pre-nidation.

KEYWORDS

Preimplantation development, embryo and hatchling, prenid, prenidial thermoregulation, incubator care, in vitro fertilization

INTRODUCTION

Prior to implantation, infants are free of attachment to the maternal body and are of a small size. Consequently, preimplantation infant care is amenable to the application of integrated microfabrication technologies (IMT). IMT technologies are able to produce integrated electrical, mechanical, and chemical systems and devices at the submillimeter, micrometer (micron), and nanometer scale. A few examples of IMT technologies include micro-electro-mechanical systems (MEMS), complementary metal oxide semiconductor (CMOS) technology, and nanotechnology. [1] By employing microfabrication technologies in combination with large-scale technologies, the medicine-of-the-future will be able to care for the preimplantation patient in a sophisticated micro-milieu.

Because preimplantation infants are amenable to specialized care, it is important to have a convenient terminology to refer to them. A child prior to implantation is called a prenid ("PRE-nid"), a word derived by shortening of pre-nidation. The word prenidial ("pre-NID-e-al") means pertaining to prenids or to life before implantation.

Prenids fall into two categories: embryos and hatchlings. Prenids prior to hatching are termed

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embryos; prenids after hatching are termed hatchlings. Historically, note that a lack of understanding of the human hatching behavior resulted in an incorrect application of the term embryo, for it was once mistakenly thought that a fertilized egg simply "attached" to the uterine wall. As a result embryonic life was mistakenly assigned to an arbitrary length of time, rather than exclusively to life before hatching. Instead, it is now realized that an infant must literally hatch before implanting. [2]

Correctly understood, hatching is an early human behavior, observable when an embryo breaches the eggshell. Note that surgically assisted hatching, in which holes are surgically made in the eggshell in anticipation of hatching, confirms the animated nature of the hatching behavior, since an exit based on a pressure mechanism would be impossible when multiple holes are made present in the shell. [3-5] This understanding should be clear from the standpoint of biophysics, for notably the embryo would be unable to prefer one hole over another based on a pressure mechanism, and even so back pressure would escape through an opposing hole, thus making it impossible to hatch without involving actual movement. Consequently, hatching is correctly understood as a human behavior involving a type of movement.

It may be inferred that the basis for such movement is contained at the molecular level within cells. Also inferred is that hatching infants rely on molecular computing inside their cells for brain power, it being implied that brain power is rooted in molecular computing, and that the neurons formed later are simply differentiated as interconnects. Although the circumstances of the hatching behavior indicate that these inferences are more than mere hypotheses, it should not be surprising that along with advancing care for the prenidial infant is coming the knowledge to dispel old myths. This knowledge can be substantiated and improved by those who accept high technical standards.

In the past, under the auspices of in vitro fertilization, incubator care for prenidial infants has been plagued by low technical standards involving crude laboratory methods suitable for only the most primitive biological specimens. [6] Myths and prejudices combined with social and religious anxieties have impeded our progress. [7,8] A new trend in reproductive biology is to research development of a sophisticated micro-milieu for prenidial infants based on recent advances in IMT technology. Consequently, the age of a sophisticated incubator for prenidial infant care is now on our horizon.

PRENIDIAL THERMOREGULATION

A chief error in the development of the neonatal incubator was that physicians failed to account for the changing endogenous (internal) heat production of the infant due to growth; thus, early incubators faltered for failure to monitor body temperature and to thermoregulate accordingly. [9] Unfortunately, history has repeated itself with the advent of in vitro fertilization, for in this case practitioners have confused the temperature of the inside of an incubator, as measured by an incubator thermostat, with a measure of the true body temperatures of prenidial infants inside.

Simply put, practitioners did not appreciate the physical distinction between the body temperature and an environmental thermostat reading. Since the incubator creates a room-type microenvironment for the prenidial infant, confusing the incubator thermostat reading with a measure of body temperature is the same as confusing a wall thermostat reading of room temperature with a measure of someone's body temperature in the room. Instead, it is well known that a patient thermometer must be used to take the patient's body temperature separately, and that this variable is physically distinct from the variable of room temperature.

Thus, to improve regard for this understanding, it appears there needs to be some review of the fact that thermodynamics applies equally to microscopic and macroscopic dimensions. Since prenids produce heat endogenously, the temperature of the prenid's environment will need to be cooler than the body temperature in order for heat to be dissipated at steady-state equilibrium. This is true because heat flows downhill in terms of the thermal gradient. It is this gradient of heat dissipation that implies an inherent physical distinction between a prenid's temperature and the incubator temperature. Also, given two embryos in equally sized eggs in the same environment, in terms of a steady-state equilibrium the one with the greater endogenous heat production will have the higher body temperature, even though the environmental temperature is the same for both. Finally, as the capacity for endogenous heat production increases, for example due to size increase based on growth, the body has a greater potential to become overheated unless properly thermoregulated.

For these reasons, it is evident that body temperature must be monitored distinctly from the incubator thermostat which monitors incubator temperature. A solution to this problem has been recently described in U.S patent no. 6,694,175. [10]

According to the techniques of infrared microthermography, an infrared camera is fitted with a microscope lens, or is attached to a microscope, and the body temperature of the prenidial infant is monitored and measured distinctly from the temperature of the fluid incubation medium in which the infant is kept inside the incubator. In this way infrared microthermography is used to focus in on each infant's temperature as distinct from the temperature of the infant's microenvironment as established by the incubator.

Once the body temperature is measured, thermoregulation can be achieved using a feedback loop to control temperature. For fine temperature control, infrared light emitting diodes (IR-LEDs) are employed in the same way that an infrared heat lamp is used to keep a neonate warm. In other words, prenids are so small that an IR-LED serves as a heat lamp to keep the patient's body warm. In a prenidial incubator the fluid incubation medium is kept slightly cool to allow heat dissipation and to serve as a buffer against the patient's temperature getting too high. In turn, the IR-LEDs supply the remaining amount of heat and are continuously cycled by computer controls in relation to body temperature measurements so as to maintain the optimal temperature for the infant.

The taking of a patient's temperature as an indicator of health is one of the most basic practices of modern medicine. Additionally, accurate temperature-taking of the body temperature is essential for accurate thermoregulation, and accurate thermoregulation forms the basis of a competent incubator system. For this reason, the ability to monitor body temperature correctly and to thermoregulate accurately has hailed an advanced age of incubator care for the prenidial infant.

AN EMERGING TREND

Technical standards in the field of in vitro fertilization were initially approached with apathy because mortality rates were so high that it led practitioners to depreciate the dignity and worth of the prenidial infant. This tragic situation is paralleled historically by social views on the status of postpartum infants prior to the advent of pediatrics.

Harvard University's late pediatric historian Thomas E. Cone, Jr. explains that infant mortality was once considered unfortunate but inevitable due to very high rates of mortality and a lack of advancement in infant care. For example, he notes that Queen Anne (1665-1714) gave birth seventeen times yet the longest survivor died as early as his eleventh year, and similarly that but one of Thomas Jefferson's (1743-1826) six children survived him. In other words, very high mortality rates were once common even among the wealthy and educated. Cone further reflects that the historian Edward Gibbon (1737-1794) noted in his *Memoirs* that "the death of a newborn child before that of its parents may seem an unnatural, but it is strictly a probable event, since of any given number born the greater number are extinguished before their ninth year. Without accusing the profuse waste or imperfect workmanship of Nature I shall only observe that this chance was multiplied against my infant experience." [11]

Unfortunately, similar apathy lingers on even today regarding what some view as "strictly a probable event" of mortality, to quote Gibbon. For example, having achieved only low technical standards for the care of the prenidial infant, the American Society for Reproductive Medicine (formerly the American Fertility Society) parallels this historical apathy by rationalizing that "the potential of a given zygote for full development is both statistical and conditional" in view of very high mortality rates. [12] Similarly, many adherents of religion or science have been queasy about affirming the early life of the person, for fear they will be accusing God or Nature of "profuse waste or imperfect workmanship" in view of very high mortality rates, again to quote Gibbon. Also, medical professionals have been insecure about their role in prenidial infant care. [13]

In contrast to these unproductive reservations, history and wisdom teach that our human calling is to subdue these trends of untimely mortality with advancements in care. For it was precisely on this basis that the discipline of pediatrics, established in the late 1800s, transformed the world in this regard. In a similar way, conceptiatrics ("con-sep-tee-AT-riks"), a word derived by combining conceptus with the accepted suffix –iatrics, is gradually emerging as the specialty of the child in gestational life. Thus, conceptiatrics endeavors to accomplish for children before birth what pediatrics has done for children afterwards. Prenidial medicine is a branch of conceptiatric medicine to treat of the child before implantation, whether in the context of incubator care or natural gestation.

The emerging trend of improving incubator care for the prenidial infant follows advancements in microfabrication technology. Key technical improvements in prenidial incubator development have emerged in the areas of thermoregulation, fluidic ventilation, and microcradle development. Fluidic ventilation means a slight flowing of the fluid incubation medium over the patient's body to refresh needed substances and to remove wastes without removing important endogenously produced substances. A microcradle is a small size cradle for a prenidial infant; the microcradle forms the central structure in a prenidial incubator environment. The size of prenidial infants makes them particularly amenable to IMT systems and devices. In 1995 Roux et al. reported the morphometric parameters of human embryos in earliest development created by in vitro fertilization as being 157.4 microns for the outer diameter of the egg, 17.9 microns for the thickness of the shell, and 121.8 microns for the inner diameter of the egg which bounds the cells of the infant's body inside. [14] However, these parameters can vary substantially based on physical differences, maternal condition, and the way mature oocytes are made available for fertilization. The embryo will expand inside the egg near hatching time and the shell will become thinner. Hatchlings require special care because they can invade or breach structures and become attached, lodged, or lost; also, their body tissues are directly exposed. Thus, systems and devices engineered for prenidial infants must take into account various morphological, physiological, and behavioral parameters and tolerances.

In 1998 Kim et al. at the UCLA Micro manufacturing Laboratory (University of California, Los Angeles) proposed adaptation of a microcage structure for use as a microcradle. The microcage is fabricated using an IMT technology called surface micromachining. The microcage has the appearance of a sea anemone and opens and closes under the action of pneumatic pressure applied to a diaphragm under the cage. Further development is needed to reduce the size of the microcage so that it can cradle a prenidial infant. [15]

In U.S. patent no. 6,448,069 Cecchi et al. teach a picket fence structure comprising posts to keep prenidial infants separated from one another in a communal setting while in their eggs. The picket fence structure is a type of microcradle. They teach the advantage that communal life provides a mutual contribution of beneficial endogenous substances, and that the picket fence structure keeps the infants separated for track-keeping purposes. But they do not incorporate a ventilation system with their structure for the purpose of fluidic ventilation. [16]

In U.S. patent no. 6,673,008 Thompson et al. teach the necessity of fluidic ventilation for prenidial development in likeness to the fluidic ventilation provided by the fallopian tube. They rely on a well-type structure with a microporous floor to keep an embryo housed at the bottom of an enclosed tank. [17] Campbell et al. in published U.S. application no. 2002/0068358 also teach a well for housing an embryo. [18] The teaching of Beebe et al. in U.S. patent no. 6,193,647 somewhat appreciates the necessity of fluidic ventilation, however, their appreciation appears to be compromised by their objective of employing fluid flow to roll the eggs of embryos; consequently, the rate of fluid flow they suggest appears to be much too harsh by several orders of magnitude. They teach both well-type and channel-type structures for housing an embryo. [19]

The present author teaches a vented microcradle (patent pending) comprising a vented flooring surrounded by a picket fence enclosure. A grill-like pattern of vias in the flooring provides fluidic ventilation by means of associated microfluidics underneath. Microfluidics is an IMT technology for applying small-scale fluid flow. As is the case for a neonatal incubator, the cradle portion of a prenidial incubator must allow for easy access to a patient while at the same time affording proper thermoregulation and ventilation at all times; the vented microcradle satisfies these objectives. Additionally, the associated microfluidics can be used to channel fluid samples for chemical analysis and in conjunction with delivery of treatments. The vented microcradle can be made of glass using chemical etching, laser etching, and ion-beam etching. The advantage of glass is that the properties are inert, whereas more exotic materials have yet to be researched for any possible harmful effects to a developing infant.

Although there is an emerging trend of improving technical standards in the area of prenidial incubation, in many instances there still remains a taint of apathy regarding the need to recognize the dignity and worth of the person. In this regard, sometimes technical improvements are contradicted by a lack of human improvement. Nevertheless, the trend of both technical and human improvement is emerging. Notably, U.S. patent no. 6,694,175 is the first invention for prenidial infant care to be classified with incubators for premature infants (current U.S. classification 600/22). This is because, with proper human and technical understanding, prenidial infants in incubators are indeed premature infants because it is premature for them to be outside the maternal body. [10]

Finally, it may be noted that in vitro fertilization technically refers only to the act of fertilization taking place in vitro. In contrast, the care of the child outside the maternal body regards prenidial incubation. Prenidial incubation promises application beyond use with in vitro fertilization. For example, if the mother dies in an accident and the means to detect her prenidial infant becomes available, the infant can be transferred to a prenidial incubator to await transfer to an adoptive mother. Similarly, if the mother's fallopian tube is found to be blocked or she requires treatments that might harm the infant, the child can be transferred to a prenidial incubator and then either transferred back or transferred to a surrogate mother. Thus, there is every reason to support the emerging trend of advancing care in the development of prenidial medicine and incubation. [20]

CONCLUSION

Advanced technology is making it increasingly possible to provide sophisticated incubator care for the preimplantation patient. A key step in this direction is provided by the advent of accurate thermoregulation techniques. Prenidial incubators may be likened to neonatal incubators, except they are for prenids instead of for neonates. There is a need for doctors and nurses to be trained in prenidial medicine.

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