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Reproductive research in non-human primates at Institute of Primate Research in Nairobi, Kenya (WHO Collaborating Center): a platform for the development of clinical infertility services?

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The Institute of Primate Research (IPR; www.ipr.or.ke) is a WHO collaborating center for research in reproductive biology, infectious diseases and ecology/conservation. It includes a fully equipped surgical complex, >5000 square feet of laboratory space, a quarantaine facility, library, conference room, administrative offices, etc. More than 500 primates can be housed at IPR, mainly baboons. Reproductive research at IPR is applied to endometriosis, assisted reproduction, prevention of heterosexual transmission of HIV and includes the investigation of immunocontraceptives and placental retroviruses. Reproductive research capacities of IPR include: videolaparoscopic surgical equipment, surgical experience, endometrial biopsies and uterine flushes, ovarian stimulation, laparoscopic oocyte aspiration, hormonal analyses in baboon blood and urine, sperm assessment, *in vitro* culture and reproductive immunological investigations. During the last years, simultaneously with the development of baboon IVF, there have been contacts with several Kenyan gynecologists at the level of KEMRI (Kenya Medical Research Institute), KOGS (Kenyan Obstetrical and Gynecological Society), Kenyatta National Hospital and Aga Khan Hospital in Nairobi to develop clinical infertility services including low-budget high-quality IVF in Nairobi. The logic behind this initiative is that the Kenyans trained in non-human primate embryology, and IVF would be natural partners to develop human IVF in Kenya.

Keywords: infertility; baboon; non-human primate; endometriosis; poor resource countries

Introduction

One in four ever-married women of reproductive potential in most developing countries is infertile because of primary or secondary infertility (DHS Comparative Report 9). The WHO has defined the provision of high-quality services for family planning, including infertility services as a core element of its policy in reproductive health for low-resource settings.

Available data indicate that countries in sub-Saharan Africa have some of the highest rates of infertility in the world. Infertility rates among married couples in African countries range from 15% to 30%, compared with reported rates of 5–10% in developed countries (Okonofua, 2003). There is now conclusive evidence that much of the infertility in Africa is attributable to infections that produce irreversible reproductive tract damage in men and women (Okonofua, 2003). Recently, it has also been shown that also endometriosis may contribute as well to infertility in African countries, even though its true prevalence is underestimated (Kyama *et al*., 2007a). Apart from the share size of the problem, it is also now well known that infertility in African countries has severe negative consequences for women's reproductive health. Owing to the high cultural premium placed on childbearing in many African countries, infertility often poses serious social problems for couples (Okonofua, 2003). Normally, women are more severely affected than men, even when the infertility is due to a male factor, often leading to divorce, social ostracization and sometimes physical abuse of women. Consequently, there is now a growing body of scientific opinion that suggests that addressing infertility could be one way to empower women in Africa and improve their sexual and reproductive health (Okonofua, 2003).

The aim of this paper is to provide a review about the Institute of Primate Research (IPR), Nairobi, Kenya (www.ipr.or.ke), a

WHO collaborating center, to describe reproductive research in endometriosis and assisted reproduction carried out at IPR during the last 18 years, and to discuss how this reproductive research at IPR can be a platform for the development of clinical infertility services in Nairobi.

IPR, Nairobi, Kenya: a WHO collaborating center

The IPR was started in 1960 by L. Leakey at Tigoni, a primate holding facility in the neighborhood of Nairobi, to support research in primate behavior as a model for the study of human evolution. In 1983, IPR was relocated to the indigenous Ololua forest (500 acres of land) in then Nairobi suburb of Karen, ~20 min drive from the center of Nairobi and ~40 min drive from Nairobi Jomo Kenyatta International Airport. The IPR is part of National Museums of Kenya (NMK) and is therefore a Kenya Government Institute. Over the last 25 years, the IPR has gradually transformed into a Biomedical Research Institute with major research programs in reproductive biology and health, tropical and infectious diseases, and ecology and conservation biology. The mandate of IPR is to support investigator-initiated biomedical research in non-human primates as preclinical models for important human diseases (including preclinical testing of new drugs, vaccines and diagnostics), and to generate scientific knowledge on the behavior and ecology of non-human primates as a basis for their conservation in the context of biodiversity.

At a global level, research capacity building of the IPR in Nairobi, Kenya, or in other poor resource countries could and should be seen as relevant effort in the context of North–South collaboration with the ultimate goal to develop international research centers of excellence in these countries (D'Hooghe *et al*., 2008).

The IPR is led by the IPR Director and is supervised by Secretary-General of the NMK, who represents NMK and IPR at the Board of the NMK. The IPR International Advisory Board (IAB) has been established in 2007 by IPR and NMK to advice IPR on its policy with respect to research, grant applications, international collaboration and research opportunities for Ph.D. students and for post-doctoral fellows both in Kenya and abroad. Furthermore, the IPR IAB is expected to advice IPR on how it can achieve institutional sustainability by, for example, assisting with the development of institutional grants that can be used to improve laboratory and animal facilities and acquire equipment. The IPR IAB includes 12 international experts who have an established reputation in the areas of reproduction, infectious diseases and ecology/conservation and a WHO observer, and meets at least once a year in Nairobi.

The total staff at IPR (status 2007) consists of 120 employees including 35 scientists at Ph.D. or M.Sc. levels, 5 veterinarians, lab technicians and supporting staff. The Department of Animal Resources is responsible for animal welfare, colony management, non-human primate medicine and surgery, quarantine, histopathology and diagnostics. The Department of Finance and Administration takes care of Human Resources, Physical Operations, Accounts, Information Technology, Library and Supplies. Research projects are reviewed by the Institutional Review Board with respect to both ethical issues and animal welfare.

Non-human primates kept at IPR included mostly baboons (mostly Olive baboons, a minority of Yellow baboons) captured from the wild, and some vervet monkeys.

The program of ecology/conservation is aimed at the study of Colobus monkeys and De Brazza monkeys, an endangered species in the Tana River Natural Primate Reserve and in Kakamega Forest, respectively. The program of infectious diseases has developed both baboon and vervet monkeys as models for the study (immunology, preclinical vaccine and/or drug development) of schistosomiasis, leishmaniasis, malaria and SIV.

Reproductive research at IPR: the advantages of the baboon model

The use of the baboons as preclinical research models in reproductive research is supported by the Kenyan government as one of the methods to mobilize national resources in order to improve human reproductive health. The baboon is a unique preclinical model for research in human reproduction for various reasons, as reviewed before (D'Hooghe, 1997, 2008; Kyama *et al*., 2007b).

Reproductive anatomy, endocrinology and physiology is similar in baboons and in humans

The baboon is comparable to women with respect to cycle length (33 ± 2 days); duration of menstruation (3 ± 1 days); time interval between LH peak and menstruation (17 ± 1 days); maximum serum estradiol level attained per cycle (245 ± 30 pg/ml) and maximum serum progesterone level attained per cycle (11.5 ± 2 ng/ml) (Stevens, 1997). The baboon pregnancy lasts ~6 months. Baboon placentation is in some ways comparable with and in other ways different from placentation in women and in rhesus monkeys (Pijnenborg *et al*., 1996).

Non-invasive cycle monitoring based on perineal changes

In baboons, but not in rhesus monkeys or in cynomolgus monkeys, is it possible to perform non-invasive perineal skin monitoring to determine the phase of the menstrual cycle in baboons. Perineal inflation and deflation correspond with follicular and luteal phase, respectively, whereas ovulation occurs ~2 days before perineal deflation (Stevens, 1997). This perineal monitoring is performed by trained animal attendants at the IPR on a daily basis, and this allows the detailed follow-up of individual baboons over a long period of time (D'Hooghe *et al*., 2008).

Continuous breeding

Baboons have continuous breeding in captivity (Birrell *et al*., 1996), in contrast to the seasonal breeding observed in rhesus monkeys (Zondervan *et al*., 2002). This advantage allows investigators to carry out fertility throughout the year and saves costs (D'Hooghe *et al*., 2008).

Baboon size and strength

Adult female baboons are stronger and larger (8–15 kg) than adult female rhesus monkeys (4–11 kg) or cynomolgus monkeys (3–7 kg) (Einspanier and Gore, 2005; Hunnell *et al*., 2007). This advantage allows repetitive blood sampling, repetitive laparoscopies (every 2–3 days) and complex experimental surgery (D'Hooghe *et al*., 1996a).

Spontaneous peritoneal fluid

Baboons, but not rhesus monkeys or cynomolgus monkeys, do have spontaneous presence of peritoneal fluid (PF) in sufficient amounts (~2 ml after ovulation) to be used for research. This is important since the peritoneal cavity and PF are key players in the pathogenesis of endometriosis (D'Hooghe *et al*., 1991).

Cross-reactivity between baboons and humans

Owing to closely shared genetic similarities between baboons and humans, cross-reactive human steroid assays, antibodies or PCR primers can be used in baboons in the context of research in endometriosis or other reproductive disorders (D'Hooghe *et al*., 1996b, 1999, 2001a,b,c, 2008; Fazleabas *et al*., 2003; Overbergh *et al*., 2005; Kyama *et al*., 2007c).

Vaginal transcervical uterine access

In baboons, but not in rhesus monkeys or in cynomolgus monkeys, it is possible to have relatively easy vaginal transcervical access to the uterine cavity allowing endometrial biopsy, embryo transfer, preimplantation embryo flushing and hysteroscopy (D'Hooghe *et al*., 1996c, 2004; Chai *et al*., 2007; Nyachieo *et al*., 2007). If routine uterine access via a vaginal speculum is difficult, combined abdominal–cervical manipulation (the Chai technique) allows transvaginal uterine access in nearly all cases (Chai *et al*., 2007; D'Hooghe *et al*., 2008). Alternatively, endometrial biopsy is also possible by transabdominal insertion of a Novak curette through the uterine fundus under direct laparoscopic control (Nyachieo *et al*., 2007; D'Hooghe *et al*., 2008).

Development of the baboon model for research in endometriosis at IPR

Since 1990, the baboon model for endometriosis has been developed at the IPR, a WHO collaborating center in Nairobi, Kenya, where research in NHP reproductive disorders can be done at an affordable cost while maintaining high ethical standards (D'Hooghe *et al*., 2008). Baboons do have spontaneous retrograde menstruation (D'Hooghe *et al*., 1996d), display human-like minimal to severe spontaneous endometriosis (D'Hooghe *et al*., 1991; Cornillie *et al*., 1992; Coe *et al*., 1998; Dick *et al*., 2003), offer an *in vivo* culture model for endometrial–peritoneal interaction and develop induced endometriosis within 25 days after intrapelvic injection of menstrual endometrium (D'Hooghe *et al*., 1995). The baboon model also allows the study of the spontaneous evolution of both spontaneous and induced endometriosis by serial laparoscopies with detailed and repeated quantitative pelvic assessment of endometriosis, according to the classification system of the American Fertility Society/American Society of Reproductive Medicine which has been adapted for use in the baboon (D'Hooghe *et al*., 1995, 2006; Falconer *et al*., 2006; Lebovic *et al*., 2007). The baboon model has been used to test new drugs for treatment or prevention of endometriosis (Barrier *et al*., 2004; D'Hooghe *et al*., 2006; Falconer *et al*., 2006; Lebovic *et al*., 2007) and is important to test general and reproductive safety of new anti-endometriosis drugs (D'Hooghe *et al*., 2006, 2008; Falconer *et al*., 2006). The baboon model has also been developed for standardized and controlled fertility studies while controlling for the presence of endometriosis (laparoscopy assessment), ovulation (monitoring of the perineal cycle), for sexual activity (observation of timed intercourse with male baboon and post-coital test) (D'Hooghe *et al*., 1994, 1996e) and for male factors (males of proven fertility with a normal sperm analysis) (Amboka and Mwethera, 2003). Endometriosis-associated subfertility has been observed in baboons with mild, moderate or severe endometriosis (spontaneous and induced), possibly related to an increased incidence and recurrence of the Luteinized Ruptured Follicle Syndrome, in the absence of ovarian endometriotic cysts (D'Hooghe *et al*., 1996c, 1997).

Development of the baboon model for assisted reproduction at IPR

The need for non-human primate models is increasing due to ethical constraints of reproductive research in humans and to increased public awareness about the safety of new developments in assisted reproductive technology. All biomedical issues related to conception and early human life are bound to be scrutinized and analyzed critically, not only by physicians or scientists, but also by ethicists, sociologists, politicians and the media. In contrast, it is generally accepted in biomedicine and by the public opinion that new diagnostic or therapeutic methods in reproductive medicine should be safe and efficient before application in humans (Schatten, 2002; Winston and Hardy, 2002). There is concern about the efficiency and the safety for nearly all new reproductive technologies that are being developed or already applied in humans, especially regarding genomic imprinting and premature exposure of gametes and embryos to potentially damaging growth factors from *in vitro* culture media. The health of children born after these techniques and their impact on future generations is of course very important. These concerns are related to intracytoplasmatic injection of immature or abnormal sperm, spermatogonial stem cell transplantation, *in vitro* oogenesis and maturation, embryogenesis after cryopreservation and thawing of immature and mature oocytes, development of new culture media for long-term culture and their effect on embryo quality, clinical application of embryonic stem cells, therapeutic cloning, the efficacy of new cryopreservation techniques, etc. The practice of cytoplasmic transfer for the treatment of 'infertility related to cytoplasmatic dysfunction in older women' has been introduced in clinical practice without significant tests regarding safety and efficiency (Barritt *et al*., 2001). This assessment of safety and efficiency is difficult since human reproduction is a unique biological process, fundamentally different from reproduction in rats,

mice, rabbits or even pigs, goats or cattle. Only non-human primates like the great apes (chimpanzees, gorilla, urang-utans), baboons and rhesus monkeys are in most aspects similar to humans in terms of reproductive anatomy and physiology. In fact, it is not surprising that some reproductive diseases, like endometriosis, only occur in non-human primates and not in other animals (D'Hooghe, 1997). Only in rhesus monkeys, procedures for ovarian stimulation, oocyte aspiration, IVF, intracytoplasmic sperm injection (ICSI), embryo culture and embryonic stem cell derivation have been well established (Thomson *et al*., 1995; Stouffer and Zelinski-Wooten, 2004). However, most rhesus monkeys are committed to research in infectious diseases (Sauermann, 2001; Bavister, 2004), which increasingly limits their availability for reproductive research. Although great apes such as the chimpanzee and gorilla are phylogenetically closer to humans (1.5% genome difference), as well as in terms of reproductive anatomy and physiology, they are endangered species and therefore not widely used as experimental animal models for reproduction (D'Hooghe, 1997; Taylor *et al*., 2002). The baboon offers an attractive alternative, as it is not an endangered species but an agricultural pest in many Sub-Saharan African countries. Therefore, it is ethically acceptable to consider the baboon as a research model for human assisted reproduction studies, since this is a medically and ethically important process that cannot be studied in a clinically meaningful way in other animal models (D'Hooghe *et al*., 2004). The baboon has also been validated for intrauterine research (Chai *et al*., 2007).

Results achieved so far at IPR have shown that this baboon model is useful for assisted reproductive studies. Indeed, various ovarian stimulation procedures have been tested and optimized, gamete procedures established and *in vitro* fertilization (IVF) procedure optimized (D'Hooghe *et al*., 2004; Nyachieo *et al*., 2008). Both classical *in vitro* fertilization and ICSI have been evaluated and are being used (Nyachieo *et al*., 2008). We view that the availability of this model may assist in addressing the raised concerns in human assisted reproduction and infertility issues. This research provides the basis for the study of embryo development, uterine implantation after *in vivo* and *in vitro* fertilization, test the safety and efficacy of currently introduced cryopreservation techniques as well as the study of embryonic stem cell development in baboons and generation of genetically identical baboons by morula splitting (Liebermann *et al*., 2003; Bavister, 2004).

Development of the baboon model for heterosexual transmission of SIV at IPR

At present, several research teams at IPR have started to develop the baboon model for heterosexual transmission of SIV and related viruses. This model could be very important to evaluate several local vaginal microbicides in their capacity to prevent this heterosexual transmission.

Cost and ethics

As per 1 November 2007, the cost for baboon research at the IPR is $450 for purchase, $3 per diem and $60 per hour of surgery, as is listed on the IPR website at www.ipr.ke. The cost for a proof of concept randomized controlled trial in order to test a new drug in the prevention of endometriosis in 15 baboons during 3 months can be estimated to be <$100.000 (D'Hooghe *et al*., 2008).

Baboons are not an endangered species but represent a threat to agriculture in Sub-Saharan Africa and are often killed by local farmers. Baboon research at IPR has the advantage that the baboons live in their natural habitat, usually in group cages that allow them to maintain their social structure as much as possible. Baboons, like other NHPS, are the only clinically relevant animal models in endometriosis research that allow the study of cause–effect relationships, since they are the only species with spontaneous or induced endometriosis similar to the disease in women. In the view of the wide phylogenetic gap between rodents and humans, and the fact that the baboon model is well established, it can even be argued that it is unethical to test a new endometriosis drug in women before safety and efficiency for this drug have been established in baboons (D'Hooghe *et al*., 2008). However, it is very important that any baboon research carried out at the IPR in Nairobi, Kenya, meets the highest possible standards with respect to scientific excellence and animal welfare. Therefore, it can be recommended to seek double ethical approval for reproductive research studies in baboons both from the Ethical Commission at the IPR and from the Ethical Commission of the institution where the scientific collaborator is working (D'Hooghe *et al*., 2008).

How can the scientific expertise in reproductive research at IPR be translated into the establishment of high-quality and affordable infertility services for the Kenyan people?

On the basis of the information presented above, it is clear that IPR represents a Kenyan Institute with established expertise in research in reproduction. The Kenyan National Center for Research in Reproduction (NCRR) includes not only IPR but also the Department of Obstetrics and Gynecology at Nairobi University/Kenyatta National Hospital and the Department of Animal Physiology at the Department of Veterinary Sciences at Nairobi University. This NCRR could represent the platform to translate the reproductive research capacity present at IPR to the provision of high-quality and affordable clinical infertility services in a poor resource setting. This is important since there are no infertility services available in the public sector in Kenya. At least one private center is active in the Nairobi area, but treatment costs are high and Kenya has not yet put in place systems of quality control and/or accreditation for centers of reproductive medicine. Most Kenyans with infertility, who can afford it, travel to South Africa or to the EU for treatment.

Over the last few years, the authors of this paper have taken several initiatives to develop clinical infertility services in Nairobi. These contacts have included: informal contacts with Kenya gynecologists (Kenyatta National Hospital, Nairobi Hospital and Aga Khan Hospital), a site visit/meeting with the Director of Kenyan Medical Research Institute (KEMRI) followed by a written action plan involving

a Leuven–KEMRI collaboration, and current plans to organize an Infertility Workshop in collaboration with the International Federation of Fertility Societies (IFFS) in Nairobi in the near future. The following challenges/questions will have to be addressed in the future:

(i) identification of enthusiastic young gynecologists interested in offering high-quality/low-cost infertility services including assisted reproductive technology (ART);
(ii) set-up ART as part of a center/network of reproductive medicine offering all diagnostic/treatment options;
(iii) how to develop a win–win situation for both gynecologists and patients in and alliance between private and public sector.

There is little doubt that, in order to be successful, the development of high-quality, low-cost infertility services in Nairobi will require a good business plan with respect to personnel training; quality assurance, protocols, SOPs; communication; work planning; electronic systems for records and data management (computer compatible from the start); data evaluation; ... as has been proposed in another paper of this Monograph (Cooke, 2008).

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