Product development specifications for a follicular sampling device for use in a human in-vitro fertilisation clinic

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Abstract:

The likelihood of pregnancy in human *in-vitro* fertilisation is heavily dependent on the condition of the embryos that are re-implanted into the patient's uterus. The condition of embryos is in turn dependent on the quality of the oocytes, from which they grew. It has been suggested previously that oocyte quality could be related to the level of dissolved oxygen in the ovarian follicle. The first objective of this work was to develop a set of product development specifications for a device that would be used routinely in a fertility clinic for sampling follicular fluid for dissolved oxygen determination. The second objective was to design and construct a prototype so that the relationship between dissolved oxygen and oocyte quality could be established.

A length of time was spent at two fertility clinics, one in Hamilton, New Zealand and one in Auckland, New Zealand. The experiences at these clinics, as well as technical constraints, were translated into a set of product development specifications. These specifications canvassed issues relating to cleanliness, potential damage to the oocyte and preservation of the dissolved gas equilibrium in the sample. A prototype device was designed and developed and found to be wanting in the clinical environment. Further clinical constraints were identified from this experience, allowing a second prototype device to be developed. This second device was found to be suitable for clinical use and it is anticipate that in the future the sampling device will re-emerge in a new, more suitable form, based on the specifications developed in this thesis.

Measurements of intra-follicular dissolved oxygen are on-going.

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I would like to thank the Beatles for the White Album.

The research for this thesis was approved after consideration by the Waikato Ethics Committee.

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Chapter 1. Introduction

Earth's increase, foison plenty,
Barns and garners never empty,
Vines with clustering bunches growing,
Plants with goodly burden bowing;

Spring come to you at the farthest
In the very end of harvest!
Scarcity and want shall shun you;
Ceres' blessing so is on you.

The Tempest IV, i. William Shakespeare

While Ferdinand and Miranda had the benefit of Ceres' blessing, it is often medical intervention, rather than divine intervention that is sought in the 21st century for issues of fertility. Since the birth of a child in 1978 (Steptoe & Edwards, 1978) as a result of *in vitro* fertilisation (IVF), an entire industry has grown to supply treatment to those affected by infertility.

This thesis describes the work carried out over a 12 month period directed towards the design of a product for use in the modern fertility clinic that would allow clinicians some insight into the conditions in which an egg had developed in a patient's ovary.

In vitro fertilisation is a treatment that is used to aid couples that are experiencing difficulties conceiving. The woman is usually given hormones that encourage her ovaries to produce more oocytes (eggs) than would occur during a normal ovarian cycle. These oocytes grow inside small (up to approximately 10ml) blisters, filled with fluid on the surface of the ovaries. These blisters are called follicles. At the appropriate time a clinician will extract the follicular fluid and oocytes and the oocytes will be cultured in a laboratory. The oocytes are fertilised *in vitro* and the resulting embryos are grown further. After a few days the embryos can be implanted into the woman's uterus, frozen or discarded.

During the culture process a large proportion of embryos will develop abnormalities or die. This is thought to be an effect of the oocytes from which the embryos were grown. The quality of the oocytes is thought to be influenced in part by the supply of blood and oxygen to the follicle. So, if we know the oxygen levels in the follicle, we may be able to infer information regarding the quality of the oocyte. The effect of implanting low

grade embryos is a reduced likelihood of pregnancy and live birth. Thus, if the clinician has information regarding the oocytes, then the patient's treatment can be managed to improve the chances of a successful treatment.

1.1 Objectives

The primary objective of this project is to develop a set of product specifications that will help to guide the design of a device for sampling follicular fluid. The samples will be used to determine the dissolved oxygen content of the follicular fluid.

The secondary objective of this project is to develop a prototype device and use it in a fertility clinic. This will help to establish a correlation between dissolved intra-follicular oxygen and oocyte developmental competence, and will help to validate and refine the specifications from the primary objective.

1.2 Product specifications

Product specifications are a set of constraints that describe what a product is going to achieve. It is not a description of what the product *is* or how it works, it is a description of what it *does*. A specification is a measurable parameter that meets a need that has been expressed by a customer or identified through research.

The sampling system is to be composed of several modules (for technical reasons that are disused later in section 2.6.3). The first is the module that will interface with the surgical equipment that is used to extract the oocytes and will divert part of follicular fluid away from the bulk flow as a sample. The second part is a container that will hold the sample after it has been removed from the bulk of the follicular fluid. The third part of the system is the instrument that will be used to determine the dissolved oxygen levels in the fluid and the final part is the set of operating procedures that determines how the device will be prepared to clinical standards, used and treated after use. A detailed understanding of the physiology surrounding IVF treatment is needed in order to describe an appropriate system.