OVIDUCT MODEL OF TECHNOLOGIES OF REPRODUCTION
— Review —

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Summary

Gametic biotechnologies involve the procedures which are utilized for procuring reproductive success through the mimicry of *in vivo* events as in *in vitro* fertilisation, embryo transfer etc. With the realization that the oviduct performs most of the procedures mimiced *in vitro* under normal *in vivo* situations, the need to master the oviduct therefore, becomes paramount. The oviduct being an exocrine gland (with its output of glycoproteins) and possibly an endocrine gland must be implicated in all the preimplantational procedures of reproduction, which include ovulation, oocyte maturation, sperm capacitation, gametic and embryonal nutrition, fertilization, and implantation. The evidences in the literature for the implication of the oviduct in these processes are examined. It is concluded that there is a need for the mastery of oviductual activity in order to maximise the successes of the procedures *in vitro*, and provide gametic manipulations which will have high success rates in implantation that is the ultimate after of *in vitro* fertilization for reproductive success.
(**Key Words**: Oviduct, Reproduction, Implantation)

Introduction

Reproductive manipulations carried out in the oviduct *in vivo* must be enumerated in order to prescribe a workable model of biotechnologies *in vitro* (Ogunranti, 1988a,b). The following may be listed as tentative reproductive manipulations of the oviduct and they will be discussed:

1. ovulation
2. oocyte maturation
3. sperm capacitation
4. gamete and early embryo nutrition
5. fertilization and
6. implantation.

The view is upheld that the mastery and understanding of the procedures by which the manipulations of these processes are carried out by the oviduct will naturally lead to the mastery of the technology of reproduction.

It is customary in modern *in vitro* fertilization (IVF) programme designed to beat clinical infertility to by pass the oviduct during embryo transfer (Steptoe and Edwards, 1978; Wood et al., 1981; Edwards et al., 1980; Lopata and Wood, 1982; Trounson, 1983; Leroy and Puissant, 1988; Angell et al., 1988; Mills et al., 1992). This, however, is not the case in most animal IVF and embryo transfers (Whittingham, 1979).

Ovulation

The ovulation model of the oviduct was first mentioned by Kent (1974) when after his extensive biochemical studies, he was able to isolate a steroid produced by oviductal stroma. This steroid, from the result of his experiment, seem to be related to ovulation in the hamster since he found that salpingectomised hamsters did not have any corpora lutea as compared to the corporal lutea in control hamsters. Although report on salpingectomy in the rabbit after ovulation which was made by Alhasani et al. (1984) suggested that salpingectomy did not seem to inhibit implantation, it however seems that the effect of the oviduct on reproductive manipulations in early pregnancy is of an immediate periovulatory and perifertilization nature. The nature of anatomic connection of the oviduct of the rabbit with the ovary is different from that of the hamster and human (Del Campo and Ginther, 1972; Ginther et al., 1974). Indeed, McComb and Delbeke (1984) did infact suggest that ovulation is decreased by decreasing the number of blood vessels between the fallopian tube and the ovary in the rabbit.

In order to make our ovulation model at-

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tractive, it is also necessary to prove that in other mammals including man, salpingectomy actually disturbs the process of ovulation, since in man, this is more than likely to shed light into the presently ill understood phenomenon of the clinical condition of ovulation failure.

Oocyte maturation

The process of oocyte maturation undergoes a secondary arrest of meiosis just after ovulation which is not terminated until sperm penetration. Even though oocyte maturation, dictated by visual evidence of heterotypical division does not occur in the oviduct before sperm penetration, it might be possible that the molecular priming necessary for the attainment of full maturation takes place to some extent in the oviduct.

Tsafriri Bar-Ami and Lindner (1983) divided the process of oocyte maturation into two main stages:

1. Stage after the first meiotic arrest, which occurs just before ovulation;

2. stage during and after the second meiotic arrest, which actually takes place in the oviduct.

After the observation *in vitro* that granulosa cells cocultured with oocytes led to the arrest of meiotic resumption in the oocytes, investigators, led mainly by Tsafriri in Israel (Tsafriri, 1979) started to look for an oocyte maturation inhibitor which is thought to be elaborated by granulosa cells which presumably keep the oocytes after their primary arrest in the dictyate stage until just prior to ovulation when they resume meiosis. The postulation of an oocyte maturation inhibitor by Tsafriri and his associates (Tsafriri and Channing, 1975; Tsafriri et al., 1977), seem quite capable of explaining the fact that not all the oocytes within the ovary proceed to maturation at the same time. Their inhibitor has been partially characterised to be a peptide probably secreted by the follicular cells but the following questions still remained to be answered:

1. Where is the inhibitor produced? Presently investigators are confused as to the exact origin of this inhibitor substance. Many believe it is derived from granulosa cells (Tsafriri et al., 1977; Tsafriri, 1979; Hillensjo et al., 1979a,b), while many others are in doubt (Jagiello et al., 1977; Sato and Ishibashi, 1977) especially when tissues of bovine, porcine or ovine granulosa cells were utilized for study. It may well be produced in the oviduct.

2. How does the resumption of meiosis occur in the presence of this inhibitor? Do the cells that produce it shut down their production or does it's constituent molecules interact with some steroid or gonadotropin which then renders it ineffecient? We are quite sure that in *in vivo* systesms, luteinising hormone (LH) surge overcomes the inhibitory action of their oocyte maturation inhibitor (Tsafriri et al., 1983). But is it just the LH surge that does this or is it actually progesterone which it influences the lutein cells to produce?

In the elucidation of an oviduct model of oocyte maturation, the following must therefore be borne in mind:

Very classical anatomists (Pick and Howden, 1901) noted a close relationship between just one fimbria and the ovary especially in those animals that do not normally develop and ovarian bursa as in man. It has always been called the fimbria ovarica by anatomists (Willians and Warwick, 1980). Could the role of the fimbria be actually secretory in nature producing some glycoprotein substances involved in periovulatory events including resumption and maintenance of oocyte maturation at least in part?

3. The preampulla conduit has no real function except in siphoning the ova into the ampulla in order to be fertilised by the sperm cells. This conduct might therefore be easily conceived as being able to provide a milieu necessary for the molecular priming of the maturing oocyte as it slides along to its destination in the ampulla. We have demonstrated the existence of hydroxysteroid dehydrogenase in the rat oviduct occuring at the preampulla and ampulla. This means that the oviduct is steroid producing. It probably produces progesterone (Levy et al., 1992). We may then suggest an interaction of free steroid within the oviduct with the oocyte maturation inhibitor of Tsafriri (Tsafriri, 1979; Tsafriri et al., 1983) causing the formation of a complex that inactivates the inhibitor and therefore allowing the resumption of meiosis. These are exciting possibilities of implicating the oviduct in oocyte maturation. Whatever be the case, it is most likely that the oviduct in some manner allows the continued molecular maturation of the oocyte in its journey to the ampulla. Afterall, oocytes matured *in vivo* and unprimed with steroids do

not allow the formation of male pronucleus even if they resume their division after sperm nucleus penetration.

Capacitation of sperm

Two major sites for sperm capacitation have been long recognised - the uterine and oviductal milieu. The report of Zamboni (1972) suggest that the uterotubal junction of the mouse narrows a little after coitum made Gwatkin Andersen and Hutchinson (1972) to postulated that the oviduct is far more important in the process of capacitation of those sperm cells which are destined to fertilise the oocyte. The regions of the oviduct which perform this function has not received much attention. Yanagimachi (1969) made reference to the fact that materials from the oviductal ampulla just after ovulation can perform capacitation *in vitro*. This report was followed by the experimental report of Gwatkin, Andersen and Hutchinson (1972) which demonstrated that cumulus components of the hamster were mainly responsible for capacitation of sperm within the ampulla portion of the oviduct of that mammal.

The Gwatkin et al. (1972) observation seems plausible since investigators had earlier noticed that progesterone priming of the female reproductive tract caused the loss of capacitating ability in the uterus but not in the oviduct (Bedford, 1970; Hamner and Wilson, 1972). However, since estrogen priming seems to cause increase in capacitating ability of the oviduct, it does appear that some progestogen resistant factors (probably glycoprotein) are produced in the oviduct which aid capacitation other than cumulus cells. It is therefore probably wise to study these glycoproteins and isolate the one (s) that seem to be able to cause capacitation in the oviduct. The fact that the oviduct and uterus synergistically provide the milieu for the capacitation of sperm was again emphasized by the experiment of Soupart and Clegg (1973) on the effect of leucocytic response on capacitation of sperm in the female reproductive tract.

Much more recently, Viriyapanich and Bedford (1981) conducted experiments on the endocrine factors that control capacitation in the golden hamster and they came to the conclusion that for those animals that are cyclic ovulators, progesterone and other steroids may well affect the ability of their oviducts to capacitate sperm. Their expeiment utilized the erstwhile capacitation rate assay first introduced by Chang (1959) and modified later by Soupart (1967), which involves the measurement of fertilising capacity of capacitated sperm.

The data on capacitation of the oviduct is quite illuminating to out model of spatial and temporal production of glycoproteins which are seemed useful in reproductive *in vivo* technology and raises the exciting possibility of isolating glycoprotein factors that specifically help in capacitating sperm. There is a need to obtain regional data on the ability of the oviduct to capacitate sperm (Hanmer and McLaughlin, 1974). This data must be obtained in order to allow the proper elucidation of the *in vivo* method of capacitation for applications in *in vitro* systems.

Mention should be made of the technique of xenogenous capacitation *in vitro* employed first by Iwamatsu and Chang (1969) in which cow sperm was capacitated in the oviduct fluid of the hamster. This must continue to have application in any *in vitro* systems of fertilization technology to be employed for differing animal species.

Gamete and early embryo metabolish and nutrition

The most recognised technology of the oviduct is the process of gametic and early embryonal nutrition and metabolism. Large amounts of data abound in the literature on this function and will need little discussion here. The sperm can utilize glucose in the oviduct (Olds and Van Denmark, 1957; Restall and Wales, 1966; Murdoch and White, 1968a; Hamner and Williams, 1964; Thorne and Foley, 1974) and oxygen (Iritani et al., 1969; Restall and Wales 1966; Black et al., 1968; Bravis et al., 1992; Elliot, 1974) reviewed the metabolism of the ova and developing oviductal embryos. Carbohydrate requirements of the developing embryo met by the oviduct were enumerated by Iritani et al. (1969), Friedhandler (1961), Brinster (1968) and Rienius (1970). It is also now known that glucose is a major metabolic fuel for both gametes and the oviduct it self (Bravis et al., 1972). Protein requirements were discussed by Daniel and Olson (1968), Lippes et al. (1972), Shapiro et al. (1974), Feigelson and Kay (1972) and nucleic acids as met by oviductal epithelium by Elliot (1974).

The data on steroids requirement of the early embryo is rather confusing at this moment. Since these hormones alter the composition and the rate of secretion of oviductal fluid (Greenwald, 1969; Hamner and Fox, 1969) it is possible to understand their indirect association with the developing embryo (Kille and Hamner, 1973; Weitlauf, 1971). The direct association can only be surmised from culture conditions on which sex hormones have been added. The data seem to suggest that in the very early embryo, estrogen and progesterone seem to inhibit cell division. The fact that tubal eggs do become steroidogenic have been shown by several investigators (Niimura and Ishida, 1980a,b, 1983) and also the fact that in late stages of development there is less inhibitory effect on developing eggs by steroids (Kirkpatrick, 1971). But what makes the data on early embryonal steroidogenesis most interesting is the fact that the presence of amino acids in culture reverse the antimitotic role of these steroids. The steroids also do seem to cause increase in amino acid incorporation by the protein synthesising embryo at the blastocyst stage of development (Smith and Smith, 1971).

Physical factors have been implicated in the requirements of the developing embryo. Physical contact of the embryo with oviductal epithelial cells have been cited as a possible factor in the maintenance of growth although pressure increase or changes seem to be the most plausible explanation to the effect of contact probably through the agency of mechanoreceptors present in muscularis (Elliot, 1974). There is the need for the developing egg to undergo cell to cell interactions with oviductal milieu and by so doing induce secretion of factors by the oviductal epithelial cells. Corroborative evidence for this interesting hypothesis exist in literature. Thus, Bishop (1956) found that the epithelium of rabbit oviduct seem to secrete more actively at increased pressure. Elliot (1974) reported increased development of the rabbit embryo in conditions of maximal hydrostatic pressure for the oviduct. Also Gandolfi (personal communication) have found that denuded epithelial cells of the oviduct do not secrete protein in culture unless they are provided with some agitation.

There is a need for the developing embryo of several mammalian species to be associated with factors in the oviduct and the rest of the reproductive tract in order for them to develop through all the stages of preimplantation successfully. These factors we hope to identify as probably glycorprotein factors. Elliot (1974) prefers to call them unidentified factors. The following will serve as a list of the requirements of different species for some oviducal factor (s) which have been shown to be necessarily species specific:

1. 2 cell stage block in some mouse species in *in vitro* culture system (Brinster, 1963; Whittingham, 1966).
2. 4-8 cell stage block in the rat *in vitro* culture systems (Folstad et al., 1969; Thibault, 1972).
3. 9 cell stage block in the cow (Thibault, 1966, 1972).
4. 4 cell stage block in the hamster (Bavister and Minami, 1986).
5. 9 cell stage block in the sheep (Moore and Spry, 1972).

Fertilization and very early development

The data on fertilisation in the ampulla of the oviduct is so straight forward that it might not really be too necessary to spend much time on its description.

Earlier reports indicating that fertilisation took place in the oviduct were made in the 19th century (Bischoff, 1845).

Oviducal fluid has been used extensively in the *in vitro* fertilization of animal eggs (Suzuki and Mastroianni, 1965; Suzuki and Mastroianni, 1968) although the composition of the fluid obtained experimentally is not expected to mimic the *in vivo* fluid as the physical presence of contaminants and a few other physical factors as enumerated by Gould (1974) might actually alter the chemistry especially the concentration of protein. It is however pertinent to note that the fluids collected in the usual way (Black et al., 1963) still support some measure of fertilisation of gamete *in vitro*.

In view of the fact that the oviduct can actually support fertilisation by its own fluid, Lambert and Hamner (1975) decided to investigate the fertilisation capability of some parts of the oviduct fluid. They noted earlier reports which suggested that the entire pseudopregnant period of the rabbit can support fertilization (Austin, 1948; Brown and Hamner, 1971; Bedford, 1970). They therefore designed an experiment to test

the hypothesis that the oviduct fluid can support fertilisation during pseudopregnancy and came up with the conclusion that the 2nd to 14th day of psaudopregnancy seem to have factors that support increased fertilisation rates, while the estrous fluid had factors that were detrimental. Their elegant study must however be interpreted with cuation since their experimental model did not mimic the *in vivo* as closely as possible. The interaction between the gametes and oviductal secretory cells in the intact oviduct might very well be different from what has been obtained in an *in vitro* system which has eliminated this very vital interaction with cells of the oviduct rather than just the fluid which they produce.

The recent achievement of *in vitro* fertilisation (IVF) in cows with the use of culture of gametes within the oviduct is worthy to note (Sirard et al., 1985). The modern clinical technique of gamete intra fallopian transfer (GIFT) is beginning to gain grounds as a means of beating infertility in those women with intact tubes who seem to present with idiopathic infertility or high antibody titres to sperm. The recent reports on this technique (Craft et al., 1986; Lee et al., 1986; Diamond et al., 1992; Mills et al., 1992) suggests that intra-fallopian factors in fertilisation may be of extreme importance in reproductive *in vivo* manipulations (Devroey et al., 1986). Another modification of the technique is SIFT - which is sperm intra-fallopian transfer involving the transfer of sperm into the fallopian tube during periovulatory periods, especially designed as therapeutic modality for women who have considerable sperm antibodies and will not be able to program the capacitation and transport of sperm deposited into the reporductive tract through normal copulatory process (Devroey et al., 1986). Other modification include GIFT (gamete intrafallopian transfer) and ZIFT (zygote intrafallopian transfer) in which the environment of the oviduct provides stimulus for gamete fertilisation (GIFT) and development (ZIFT) in order to achieve maximal implantation rates (Lee et al., 1986; Mills et al., 1992).

In a very recent report Brown and Cheng (1986) suggested 'our results, confirm the concept that estrus induced oviducal glycoproteins do interact with egg zona pellucida.'

Our discussion of fertilisation will not be complete without the consideration of the development of the early embryo which also require interaction with oviducal factors in order to ensure adequate programming. The report by Gaunt (1985) is important in which a teratocarcinoma factor probably produced by the oviductal epithelium becomes associated with the fertilised zygote six hours after ovulation but is absent in the *in vitro* fertilised egg until after incubation in culture for a few days. This factor may probably be necessary for the proper development of the zygote up to the preimplantation stage.

The report of Kille and Hamner (1973), as mentioned previously, in which it was shown that factors in the oviducal fluid of the rabbit on days 2, 8 and 9 enhanced the developmental capacity of rabbit embryos at their preimplantational stages is also noteworthy. Again, Stone and Hamner (1977) showed that the entire oviduct of the rabbit is essential for the proper development and subsequent implantation by demonstrating that ligation of parts of the oviduct with developing embryos *in situ* led to very low implantation rates when compared with unligated tubes all in intact animals. Their experimental design is similar to that of Adams (1973) who showed that the developing embryo of the rabbit can be supported in the oviduct till early blastocyst stage after which development becomes unsatisfactory.

Perhaps the most spectacular of the functions of the oviduct is that first shown by Whittingham (1968) in which he designed an experiment to bypass the *in vitro* development block in the mouse using explanted oviduct. This was also performed for the golden hamster with success by the use of mouse oviduct explanted in whole using the technique of zenogenous embryo culture technique by Bavister and Minami (1986). These authors were able to bypass the traditional block of the hamster egg from the four cell stage.

'Xenogenous embryo culture using the explanted mouse oviduct is a promising technique for studies on analysis of the blocks to development and for by-passing blocks in experimentally manipulated embryos.'

The causes of blockage of early embryos in culture have not been enunciated by investigators (Thibault, 1972). Brown and Cheng (1986) made mention of the fact that the pig 2 to 4 cell embryo obtained by oocyte maturation and fertilisation *in vitro* seem to have an 'absolute need for the oviduct in order to develop further.'

The block in *in vitro* systems of some animal embryos in culture may therefore be conceived as being caused by the unavailability of essential factor that program the animal embryo in a defined temporal sequence. Thus, the use of the oviduct to overcome these block suggests that the above factor is elaborated in the oviduct and that its elaboration is dependent on multicellular compartment assembly as occurs in whole explanted tissues of oviduct. Moor and his associates working in Cambridge have shown that the epithelial cells when isolated in culture do not produce any secretions and tend to differentiate and become transformed to fibroblasts whatever their spatial or temporal parameter before isolation in culture (Gandolfi et al., 1986). From their report, it therefore seems resonable to conclude that *in vitro* systems that will support the production of oviductal factors must be compartmentally multicellular and that the epithelial secretory cells are incapable of secretion without the influence of their surrounding stromal cells.

Other reports exist in the literature which tend to support the functional role of the oviduct in ensuring adequate pre-implantational development. Since the report of Hunter et al. (1962) that sheep ova can be stored in the oviduct of the rabbit and then transferred into the sheep in order to continue its growth, several other reports of this xenogenous storage and maintenance of early development using the rabbit have been made for different mammalian species. Allen et al. (1976) reported similar procedure for horse embryos. Chang (1966) did a similar study for the ferret. Polge et al. (1972) did the same for the pig and Lawson et al. (1972) made the report for the cow. Boland (1984) provided a review of this procedure and from his review it does seem that the rabbit oviduct is capable of elaborating factors that maintain the embryos of other species in the oviduct before transfer.

Adams (1973) reporting on the development of the rabbit embryo in ligated oviduct came to the conclusion that the rabbit oviduct provides the milieu for development in the rabbit till the early blastocyst stage. Kille and Hamner (1973) showed that the oviductal fluid on days 2, 8 and 9 seem to support the growth of the developing egg by a means of specific yet unidentified factor elaboration. It thus seems almost firmly established that the early embryo requires some factors from the oviduct which helps it to develop *in vivo* to the terminal preimplantational stage. The clinical report of Dvorak et al. (1985) does seem to corroborate the fact that the early embryo can be supported in the oviductal milieu since they pioneered a technique which involved the transfer of zygote fertilised *in vitro* into the fallopian tube during the time of reconstructive tubal surgery although their technique met with limited success.

Implantation

It has been shown repeatedly that the high failure rates of IVF and successful birth is mainly caused by the failure of implantation (Wood et al., 1981) and therefore the examination of implantation data and the understanding of implantation phenomenon is bound to shed some light onto the development of reproductive technology which will support a complete mastery of implantation and in clinical practice, will provide a means of control of reproduction and pregnancy at will (Edwards et al., 1985).

If we do believe that there are factors that are elaborated by the oviduct to support the eventual process of implantation, we shall have to determine what parts of the oviduct actually produce these factors. We have been able to show that other regions of the oviduct have their specialities of function as follows:

1. oocyte maturation - preampulla
2. fertilisation - ampulla
3. sperm capacitation - ampulla/junctura
4. implantation - isthmus - ampulla?

We are tempted to put down the isthmus as the site for perimplantational manipulation since the embryos for rabbit, rat and mouse spends considerable number of hours inside it possibly due to its narrow structure. We are also tempted to use the isthmus as the site of manipulation because of the Jansen report (Jansen and Bajpai, 1982) which suggests that it is the glycoproteins produced by the isthmus which is associated with the developing egg in the rabbit. But, if we consider the data in the guinea pig, human, the baboon and the rhesus monkey we might be tempted to hesitate. The developing egg spends more time in the ampulla of these species as was shown for human (Cheviakoff et al., 1976) and rhesus monkey (Eddy et al., 1975), and then for the baboon, (Eddy et al., 1976) and the guinea

glycans and other factors deemed necessary for reproductive success. It is possible to develop methods of coculture of gametes with ampullary zones to achieve high levels of fertilisation (Sirand et al., 1985) or the use of other explanted oviductal tissues to secure high rates of implantation until such a time as all important glycoproteins and deemed necessary for success are characterized

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