NAME: ANIH KELECHI FAUSTINA
MATRIC NUMBER: 18/MHS02/043
COLLEGE: COLLEGE 0F MEDICINE AND HEALTH SCIENCES
DEPARTMENT: NURSING SCIENCE

Discuss the factors facilitating the movement of sperm in the female reproductive tract

Sperm Transport through the Cervix:

In some species, the cervical canal widens under the influence of estrogen. Fluoroscopy and scintigraphy have been used in domestic dogs and cats to examine cervical patency. Opening of the cervix in these species has been correlated with estrus (Silva *et al*., 1995; Verstegen *et al*., 2001; Chatdarong *et al*., 2002). Radioopaque fluid and also human serum albumin radiolabelled with technetium 99 could be seen rapidly passing through the cervix and filling the uterine lumen after deposition in the cranial vagina at estrus.

Sperm of humans and cattle enter the cervical canal rapidly where they encounter cervical mucus (Figure 1A). Under the influence of estrogen the cervix secretes highly hydrated mucus, often exceeding 96% water in women (Katz *et al*., 1997). The extent of hydration is correlated with penetrability to sperm (Morales *et al*., 1993). Coitus on the day of maximal mucus hydration in women is more closely correlated with incidence of pregnancy than coitus timed with respect to ovulation detected using basal body temperature

Sperm transport through Uterus:

At only a few centimetres in length, the human uterine cavity is relatively small and could be traversed in less than 10 min by sperm swimming at about 5 mm/min, which is the swimming speed of sperm in aqueous medium (Mortimer and Swan, 1995). The actual rate of passage of human sperm through the uterus is difficult to determine due to experimental limitations. Variation is high among women within a study and between studies (Croxatto, 1996). In one set of experiments, fertile women were inseminated into the cranial vagina shortly before surgical excision of both Fallopian tubes. Sperm were recovered from the fimbrial segment of the ampulla in two women whose tubes were removed 5 min after insemination, even though they

had been abstinent for at least 16 days. Sperm were recovered all along the tubes of two more women merely 10 min after insemination (Settlage *et al*., 1973). Unfortunately, the motility of these sperm was not assessed; therefore, it could not be determined whether the sperm were capable of fertilizing. In another study (Rubenstein *et al*., 1951), several motile sperm were recovered from Fallopian tubes following hysterectomy 30 min after insemination in one patient and 1 h after insemination in three out of seven patients; however, these women underwent surgery for treatment of fibroids, polyps or endometriosis and therefore sperm transport may have been abnormal.

Transport of sperm through the uterus is likely aided by pro-ovarian contractions of the myometrium. Ultrasonography of the human uterus has revealed cranially directed waves of uterine smooth muscle contractions that increase in intensity during the late follicular phase (Lyons *et al*., 1991; Kunz *et al*., 1996). The uterine contractions occurring in women during the periovulatory period are limited to the layer of myometrium directly beneath the endometrium (Lyons *et al*., 1991; de Ziegler *et al*., 2001). This is in contrast to contractions occurring during menses, which involve all layers of the myometrium. In cows and ewes, electromyography has indicated that strong contractile activity occurs during estrus, while contractions are weak and localized during the luteal phase (Hawk, 1983).

In humans, contractile activity of uterine muscle may draw sperm and watery midcycle mucus from the cervix into the uterus. Fukuda and Fukuda (1994) interpreted ultrasound images of the uteri of women in the late follicular phase to indicate that the uterine cavity is filled with mucus. They proposed that the cervical mucus assists sperm movement through the human uterine cavity. This is possible because the volume of uterine fluid in midcycle women is only about 100 µl (Casslen, 1986) and cervical mucus is plentiful enough to fill the lumen.

Transport through the uterotubal junction:

The uterotubal junction presents anatomical, physiological and/or mucous barriers to sperm passage in most mammals. Anatomically, the lumen in species as distantly related as dairy cattle and mice is particularly tortuous and narrow (Hook and Hafez, 1968; Hafez and Black, 1969; Beck and Boots, 1974; Wrobel *et al*., 1993). The narrowness of the lumen is especially

apparent in living tissue (Suarez, 1987) and in frozen sections, in which tissue does not shrink as it does during standard preparation of paraffin-embedded sections (Suarez *et al*., 1997).

The entrance to the junction is fairly simple in humans; whereas, it is complicated by mucosal folds in cows, pigs, rabbits and many other species (Hook and Hafez, 1968; Hafez and Black, 1969; Beck and Boots, 1974; Wrobel *et al*., 1993). In mice and rats, the entrance forms a conical projection into the uterus called a colliculus tubarius (Zamboni, 1972; Gaddum-Rosse, 1981; Suarez, 1987).

Within the lumen of the junction, there are large and small folds in the mucosa. In the cow, mucosal folds form cul-de-sacs with openings that face back towards the uterus (Yániz *et al*., 2000). This arrangement of folds seems designed to entrap sperm and prevent further ascent.

A physiological valve may be created by a vascular plexus in the lamina propria/submucosal layer of the wall. When engorged, the plexus can compress the lumen. This plexus has been well described in cattle (Wrobel *et al*., 1993). The walls of the bovine junction and adjacent tubal isthmus also contain a thick muscular layer that could further constrict the lumen. The bovine uterotubal junction is sigmoidal in shape and supported by muscular ligaments that appear capable of increasing the flexure of the curve and thus compressing the lumen (Hook and Hafez, 1968; Hafez and Black, 1969). In the mouse, the junction is reported to be patent shortly after coitus, but to be tightly closed about an hour later (Zamboni, 1972; Suarez, 1987). The human junction traverses a thick muscular layer of uterine wall (Hafez and Black, 1969); however, it is unknown whether the muscle regulates the patency of the junction.

The narrow lumen of the uterotubal junction may be filled with viscous mucus that can impede the progress of sperm. Mucus has been found in the uterotubal junction in humans (Jansen, 1980), as well as in rabbits (Jansen, 1978; Jansen and Bajpai, 1982), pigs (Suarez *et al*., 1990) and dairy cattle (Suarez *et al*., 1997, 1990).

In rodents, it has been demonstrated that sperm with linear, progressive motility are more successful at passing through the uterotubal junction (Gaddum-Rosse, 1981; Shalgi *et al*., 1992).

Male mice that are null mutants for the genes encoding fertilin β (Cho *et al*., 1998), calmegin (Ikawa *et al*., 1997; Yamagata *et al*., 2002) or testis-specific angiotensin converting enzyme (ACE) (Krege *et al*., 1995; Hagaman *et al*., 1998) are infertile because their sperm cannot pass through the uterotubal junction nor bind to the zona pellucida. In these null mutants, both the motility and morphology of the sperm are normal. Fertilin β is localized on the plasma membrane overlying the acrosome on mature sperm from wild-type males, while it is lacking in the null mutants (Cho *et al*., 1998). As for calmegin, sequence homology indicates that it is a chaperone protein, which would place it in the endoplasmic reticulum of spermatids, assisting in the proper folding of proteins destined for membranes. Both wild-type and null mutants lack calmegin in mature sperm; therefore, its affect on fertility is presumed to be due to the lack of proteins that rely on calmegin for proper placement in the sperm plasma membrane. In the case of ACE null mutants, there is strong evidence that the missing ACE normally acts to release GPI-anchored proteins from the sperm plasma membrane (Metayer *et al*., 2002; Kondoh *et al*., 2005). Thus, the lack of ACE means that some proteins that would normally be shed from sperm are retained. These various strains of null mutant mice indicate that certain epitopes must be available and exposed on the surface of sperm to interact with the uterotubal junction and somehow promote sperm passage.

The role of calmegin in enabling sperm to pass through the uterotubal junction was examined more closely using chimeric males that produced a mixture of germ cells with wild-type and disrupted calmegin genes. The question addressed was whether calmegin-chaperoned proteins are required by individual sperm to pass through the junction, or would the presence of wild-type sperm enable them to do so. Such would be the case, for example, if the proteins on the sperm surface assist passage by signalling the junction to open. Chimeric males were created by fusing embryos from ‘wild-type’ mice that had normal calmegin genes with those from a double transgenic line of mice that were homozygous null for calmegin and expressed enhanced green fluorescent protein (GFP) in their acrosomes. The resulting chimeric XY/XY males produced a mixture of sperm, about half of which were mutant, as identified by the presence of the fluorescent acrosomes. When these males were mated with wild-type females, only wild-type sperm could be found above the junction (Nakanishi *et al*., 2004). This indicates that normal morphology and motility are not sufficient for enabling sperm to pass through the junction. An

additional factor, likely a sperm surface protein or proteins, is required by each sperm for it to pass through the junction.