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The Impact of the Pill on Implantation Factors—New Research Findings

For health consumers and health care professionals of an orthodox Judeo-Christian or Islamic tradition, as well as those authentically concerned with the universal respect of unqualified human rights, the asserted capacity of the pill to act as an abortifacient, both in its once-a-day and 'morning-after' permutations, is one of significant moral weight.

The research on 'break-through' ovulation[1,2] leads moralists, philosophers and human rights' advocates to question the use of the title 'contraceptive' to describe the pill. There is tension in this nomenclature. The term 'contraceptive' refers to a drug, device or chemical that prevents the joining of the sperm with the female secondary oocyte (commonly referred to as the ovum).[3]

The problem arises because the female sex cell, the secondary oocyte, may be present in the reproductive tract at or near the time of coitus, hence there exists the possibility that fertilization may occur. Yet, as we will see, the pill alters the receptive structure of the endometrium, making implantation problematical.

But are concerned groups justified in moving from a position which states that the pill sometimes fails to prevent 'ovum' fertilization, with the result that new human life may begin, to the position of claiming that the pill has an abortifacient capacity? The first position notes that ovulation occurs in women on the pill and fertilization may occur, but claims there is no evidence that implantation is impeded. The alternate view considers that because ovulation has been detected and the lining of the womb is in an undeveloped state, human life is imperiled.

This is a seismic shift in outlook. What merit is there in this latter claim other than supposition or suspicion? Is the pill tarnished with the title of abortifacient on conjecture rather than on fact?

This paper will seek to clarify these issues. I will concentrate in some depth on a variety of the implantation factors associated with the microenvironment of the endometrial epithelium. Discussion will also be focused on the mechanism(s) of hormonal dialogue between the 5-7 day old human embryo (the blastocyst) and the cells which line the endometrium. I will also cover the impact of above normal (supraphysiological) levels of estrogen and progesterone on these implantation factors and the role of the pill hormones on the integrity of the endometrium. Particular attention will be given to the impact of the pill on cyclical development of endometrial thickness, and the relationship of this uterine feature to the success of implantation of the human embryo. Central to these issues will be a review of the research on 'break-through' ovulation (also known as 'escape-ovulation'), an event which must occur, otherwise all concerns concerning the pill as an abuser of human rights would be shown to be empty.

This paper is of necessity detailed. I hope that the employment of suitable analogies, as well as bracketed discussion of medical terms or concepts, will make it accessible to the scholar and lay reader alike.

1.1 EXECUTIVE SUMMARY

The process of implantation of the human embryo into the lining of the womb is a very complex and delicate one.[4] Proper attachment and successful implantation is under the guidance and control of a vast array of 'implantation factors' such as interleukin-1 β (IL-1β)[5] platelet-activating factor (PAF),[6,7] insulin-like growth factor (IGF),[8] leukemia inhibition factor (LIF),[9] tumor necrosis factor α (TNF α).[10]

Many of these chemical factors participate in a process referred to in the medical journals as 'cell-signalling', a process which involves the new human embryo and the cells of the lining of the womb chemically communicating with each other.[11, 12,13,14] The purpose of this chemical communication is to create an optimally advantageous endometrial environment at the time the human embryo attempts to implant.

Aside from this bio-chemical embryo/uterine-cell communication, successful implantation of the human embryo is dependent also upon a class of molecules known as integrins. Integrins are cell-adhesion molecules found in a 'mirror' fashion on both the human embryo and the lining of the womb.[15,16] These integrins bind onto each other, via gluco-proteins (e.g. fibronectin). The success or otherwise of this binding process is intimately linked to the ongoing success or otherwise of the pregnancy.

The reader will note that I am using the orthodox understanding of the term 'pregnancy'. This definition dates the beginning of the pregnancy from the moment of fertilization. I do not use, nor do I accept the minority view,

influenced as it is by the politics of abortion, that dates a pregnancy from the time of implantation.

1.2 THE RE-DEFINING OF PREGNANCY TERMINOLOGY

Notwithstanding the embryonic, linguistic and time-honoured orthodoxy of 'pregnancy', increasingly frequent attempts have been made to redefine all aspects of pregnancy, but most particularly, when pregnancy begins. The reason for this move is clear; by redefining pregnancy—when it begins, the nature of the embryo etc—the way will be made smooth for the more rapid introduction of RU-486, the morning-after pill, anti-HCG vaccines, anti-implantation factor drugs and other embryocidal drugs. Unwittingly or otherwise, the end result is a semantically based desensitization of the moral conscience of the community.

The following is an indicative selection of quotes to illustrate my point.

> The prevention of pregnancy before implantation is contraception and not abortion.[17] (Glasier, *NEJM*, 1997)

> Predictably, some opponents of abortion allege that emergency contraception is tantamount to abortion . . . even if emergency contraception worked solely by prevention the implantation of a zygote, it would still not be abortifacient... Pregnancy begins with implantation, not fertilization . . . fertilization is a necessary but insufficient step toward pregnancy.[18] (Grimes, *NEJM*, 1997)

> Emergency contraception works by inhibiting or delaying ovulation or by preventing implantation. Despite some assertions to the contrary, it is not itself a form of abortion.[19] (Guillebaud, *Lancet* 1998)

These opinions are starkly at odds with embryology[20] and etymology.[21]

Before examining these features in more detail, and the relational involvement of the pill, it may be of some benefit to propose an analogy to assist in the understanding of the various implantation factors and the role of integrins.

Consider the example of a space shuttle, low on fuel and oxygen, urgently needing to dock with the space station. The mother ship and the shuttle communicate with each other so that the shuttle knows which docking bay to go to. Importantly, the mother ship knows which bay to make ready. Successful communication is imperative. If this electronic communication fails (disrupted embryo-uterine 'cell-talk') the shuttle may go to the wrong docking bay, fail to attach to the mother ship, drift away, with the result that the crew dies from a lack of food and oxygen. Alternatively, the shuttle might go to the right bay but find that all the docking apparatus is not in place. Again, the attachment between the two fails due to faulty communication and the crew dies. This role of embryo/endometrium communication is fulfilled by implantation factors such as interleukin, TNF, NDF and PAF. To continue the analogy, integrins could be thought of as grappling hooks that 'hold' the human embryo onto the womb whilst the process of implantation is completed.

This then is a brief overview of this review paper. I would like now to analyse these issues in more depth, looking at the specific role and activity of the main implantation factors covered in the research literature. As well, I will expand on the interaction between these factors and the steroidal hormones: estrogen, and its artificial copies (principally ethinylestradiol, ingested via the pill) and progesterone, plus its artificial copies (norethisterone, levonorgestrel, gestodene and desogestrel).

1.3 THE INTERLEUKIN SYSTEM

The interleukin (IL) system, composed of IL-lα, IL-1β and IL-Ira, is both hormonally regulated and of endometrial origin (Simon, 1996).[22] Under *normal* physiological conditions, progesterone increases the production of IL-lα, and IL-lβ from the endometrium[23] and levels of the IL system reach their maximum during the luteal (post-ovulatory) phase of the menstrual cycle.[24]

Of the various components of the interleukin system, research suggests that IL-lβ plays a key role in the proper orientation of the embryo to the uterine lining, a process known as apposition. Recalling our earlier analogy, apposition could be likened to pre-docking maneuvers responsible for correctly aligning the docking ports of mother ship and shuttle.

Within this framework, the role of IL-lβ is thought to be that of a 'signal system' between endometrium and embryo.[25] '... [S]uccess of embryonic implantation relies on a perfect dialogue between good quality embryos and a receptive endometrium'.[26]

Huang and co-workers (1997) have also reported that the IL system is 'an important factor in embryo-maternal molecular communication during the implantation process'.[27]

Whilst normal levels of the ovarian hormones estrogen and progesterone have a beneficial effect on the levels of IL-1β, excessive hormonal levels, known as supra-physiological steroid levels, have been shown to cause a reduction in the levels of IL-lβ. As a result, the rate of implantation drops significantly. Simon and co-workers *(J Reprod Immun*, 1996) have shown that there is an inverse relationship between estrogen and progesterone levels, and the levels of IL-lβ (as estradiol levels increase, implantation success decreases).[28]

The direct consequence of these findings, as they relate to the maintenance of pregnancy, are set out by Carlos Simon:

> ... we have shown prospectively that suprahysiological serum E2 (estradiol) levels during the pre-implantation period are responsible for the impairment of embryonic implantation in patients undergoing I.V.F. It is possible that above normal (supraphysiological) serum E2 levels impair implantation through disrupting regulation of uterine paracrine factors; specifically, the IL-1 system is one possible candidate when considering what is reported in the present study.[29]

The term 'paracrine' refers to the effect(s) that are caused by hormones but are localized to cells only in the immediate vacinity,[30] i.e., the endometrium, rather than the more normal, wider area of bodily influence that characterizes hormones.[31]

Simon's research indicated that excessive estradiol (an estrogen) levels interfere with implantation as a consequence of disruption to the IL-1 system. I.V.F. research has shown that high levels of estradiol (E2) result in a poor implantation rate of 8.5% whereas reduced E2 levels increased the successful rate of implantation to 29.3%.[32]

As Simon and co-workers noted, 'High E2 levels, which are known to be interceptive, and altered E2/progesterone ratios, which also are associated with the impairment of endometrial receptivity, are the main factors affecting endometrial receptivity in high responders.'[33]

The use of the word 'interceptive' is significant. Professor Rahwan, professor of Pharmacology and Toxicology, Ohio State University, defines interception as the 'interference with the implantation (nidation) of an already fertilized ovum, and, from a biological standpoint, must therefore be an early abortifacient approach'.[34]

This research by Simon finds its importance within the context of the emerging use of the pill in high doses as a post-coital or 'morning-after' pill (MAP). The MAP regime comprises the ingestion, within a time-frame of 12 hours, of approximately 10 times more estrogen and 10-20 times more progesterone than a woman would take via the normal once-a-day pill (depending on the brand used). These increased levels are obviously supra (above) physiological levels.

As previously outlined by Simon, the disruptive effect on implantation rates caused by high levels of estradiol, or incorrect estradiol/progesterone ratios, means it is biologically plausible to suggest the 'morning-after pill' (MAP) is an abortifacient-empowered medication because of its capacity to interfere with the interleukin system.

Further supporting this assertion is research by Swahn *et al.* (1996), which showed the administration of the MAP caused a suppression of the LH surge, decreased the pregnandiol levels and increased the estrone levels (Fig 1, p. 741).[35] These alterations to the normal menstrual cycle hormonal patterns had an impact on the development of the endometrium.

> An endometrial biopsy was taken one week after treatment. Although it was difficult to date the biopsy in some women because of the absence of a discernible LH peak, the conclusion was that the endometrium showed significant alterations in endometrial development with a dissociation in maturation of glandular and stromal components [36]
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> .

The authors then, in a seemingly contradictory manner, suggest that the 'relatively minor changes in endometrial development does not seem sufficiently effective to prevent pregnancy'.[37] This statement would appear to undermine any claim that the MAP acts in part via an abortifacient mechanism. Further reading reveals that the researchers did not investigate the 'biochemical effects (of the pill) on molecular levels on the endometrium'.[38] That is, the researchers did not investigate the hormonal impact of the MAP on the various implantation factors.

In my view, this omission negates their attempts to minimize the abortifacient significance of the 'relatively minor changes in endometrial development' caused by the MAP. As will be seen later, relying only on measures of endometrial thickness cannot accurately assess the precise conditions needed for successful implantation—this exclusive approach fails to take heed of the implantation factors which are the second, vital characteristic associated with successful implantation.

1.4 PLATELET-ACTIVATING FACTOR (PAF)

Another implantation factor which is associated with successful uterine receptivity of the human embryo is platelet-activating factor (PAF).[39] PAF interacts with PAF receptors located on the endometrium. To recall, receptors are bio-chemical binding sites, located on the surface of cells, which are specifically designed to interact exclusively with a specific chemical, in this case PAF. When PAF attaches to the receptor, a message is conveyed to those cells.[40]

The effect of PAF upon the endometrium is to cause a release of nitrous oxide (NO), leading to vascular dilation and increased vascular permeability of the blood vessels of the endometrium[41] The fact that chemical blockage of the PAF binding site (receptor) on the endometrium inhibits implantation supports the view that the PAF receptor has a critical role in uterine receptivity[42]

PAF is also involved in the cyclical development of the endometrium.[43,44] Not surprisingly, the levels of the receptors for PAF vary throughout the menstrual cycle, with the highest endometrial levels detected during the mid-late proliferative phase (i.e., the days preceding ovulation) and the late secretary phase,[45] when the endometrium is approaching or at its state of maximum monthly development. These findings are consistent with PAF having a preparatory role for uterine reception of the human embryo.

As was the case with the interleukin system, control of PAF is under the control of ovarian hormones, estradiol and progesterone.[46] As Ahmed has noted: 'PAF production has been shown to be regulated by ovarian hormones .. .'[47]

Given the role of ovarian hormones on the activity of PAF and its receptor within the endometrium, it is biologically plausible to suggest that irregular uterine hormone levels, caused by the pill, may have a negative impact on uterine preparedness for implantation. Supporting this view is the work of Rabe and co-workers, who reported a decrease in endometrial thickness in women taking the pill, during the days when implantation would occur.[48]

Specifically, these researchers showed that there was, for some pill users, a 50% reduction in endometrial development when compared to that seen in the control (non-pill using) group.[49] Therefore, it is reasonable to conclude there is an adverse impact upon the express of PAF receptors. Indeed, given the hormonal influence exerted by estrogen, it would be biologically illogical to conclude no damage to the expression of endometrial PAF receptors.

1.5 THE EFFECT OF MISSED PILLS ON OVULATION

For the pill to exhibit the characteristic of an abortifacient, one biological event is essential: ovulation. The crucial

question is this—does break-through (or escape) ovulation occur during regular pill ingestion?

Grimes *et al. (Obstet Gynecol,* 1994) had previously reported that 'suppression of follicular development is incomplete with contemporary low-dose pill'.[50]

Grimes' study was characterized by a high rate of patient compliance, meaning that the women involved in the study adhered to the research protocol of daily ingestion of the pill.[51] Yet, escape-ovulation was detected even within the context of a rigorously scrutinized scientific study.

These facts argue strongly in favour of escape-ovulation also occurring within the general populace of women on the pill. This latter group of women are not necessarily as highly motivated as those participating in a scientific study. To adhere to a tedious daily, monthly, yearly regime of pill ingestion, without supervision is, in the words of one feminist writer a 'bore and a chore'.[52] Because daily pill ingestion is so onerous, patient compliance will be less than the necessary ideal. However, does the occasional failure to take the pill mean that 'escape ovulation' will increase in some proportional fashion?

In an attempt to determine the frequency of escape-ovulation under more realistic conditions, researchers have constructed experiments that required women in the study to deliberately miss one or more days of the pill. A variety of tests, including ultrasound of the ovaries, estradiol (E2), progesterone (P) levels and LH (leutinizing hormone) measurements were used to determine if ovulation had occurred.

Hedon and co-workers (1992) tested 47 young, healthy women who missed between 1 and 4 days tablets starting from day 1 of a new cycle. 'None of the patients experienced normal ovulation' though one, who missed 3 tablets at the beginning of the cycle, 'had a follicular rupture', but no LH surge or progesterone increases, factors usually associated with normal ovulation[53] Note that this study was for only one cycle. Limiting the study to one cycle was a study weakness, because any follicles which may have ruptured during the normal 7 pill free days between cycles would not be detected.

Earlier, Hamilton (1989) had performed a similar study but extended the observations for two consecutive months. Of 30 women in the study, one had a probable ovulation, due to one deliberately omitted tablet on day one of the *second* cycle.[54]

More recently, Letterie (1998) published the results of a study employing a new, reduced dosage formulation of the pill. Ten women, divided into 2 groups, used two slightly different formulations comprising a delayed start, limited midcycle use of estrogen and progesterone. Each of the two treatment groups was monitored for 2 consecutive cycles. In total, 30% of cycles exhibited ovulation, all of which occurred in the *second* cycle.[55]

It is revealing to look more closely at the data for the two groups. In group one, ovulation occurred in 10% of cycles (1 in 10 cycles). This group took 50mcg ethinyl estradiol/lmg norethinodrone for days 6-10 and 0.7mg norethinodrone for days 11-19. Group two took 50mcg ethinyl estradiol/lmg norethinodrone for days 8-12, and 0.7mg norethinodrone only for days 13-21, 'five ovulation(s) occurred in 10 cycles'.[56] This is an ovulation rate of 50%. This study did not investigate implantation; all participants used barrier contraceptives, or abstinence (Private correspondence).[57]

It should be noted that these research findings, conducted under ideal research conditions, represent the best possible outcome in terms of ovulation suppression by the pill. Yet these results do not faithfully replicate real-life because they do not take into account such common events as gastro-intestinal illness or drug interactions. Stomach upset decreases drug absorption, thus loosening the hold over ovulation otherwise exerted by the pill hormones. Likewise, drug interactions decrease the amount of active pill hormone available to act in a suppressant manner upon the ovaries.[58,59] Other researchers and I are of the view that these two issues would contribute to an increase in the frequency of escape-ovulation.[60]

1.6 PILL CONTROL OVER OVARIAN FOLLICULAR DEVELOPMENT

Based upon my 20 years experience as a community pharmacist, I believe the commonly held view is that the pill fully stops ovulation (anovulation). Yet this view is wrong. The recent work by Rabe *et al.* (1997) contradicts this common misunderstanding. Following are some salient points from this research.

- Pre-ovulatory follicular cysts (> 20mm) occurred in 7.3% of 329 pill users enrolled in the study.[61] This size of follicle is identified with an increased rate of escape-ovulation.[62]
- For non-pill users, the rate of follicular cysts was 13.9%.
- Some women, notably those on triphasic formulations, had follicles measuring 60mm.
- Estradiol was present at higher levels (in pill users with enlarged follicles) than in non-pill users (who also had enlarged follicles). The respective levels were 153 pg/ml and 126 pg/ml.[63]

The estradiol level of 153 pg/ml, seen in pill users with enlarged follicles, is important, as it is close to the 'threshold level 150 to 200pg/ml', which, if persisting for approximately 36 hours, triggers ovulation.[64]

As a summary of their research, Rabe noted: 'Analysis of the ovarian activity in the current study demonstrated that the total number of developing follicles increased rather than diminished during OC use, without marked differences between OCs'.[65]

This research underscores the pill's precarious hold over ovulation suppression. It is an event endeavouring to occur. The intervention of a variety of 'lifestyle' factors such as missed doses, drug interactions or gastro-intestinal upset, can act to loose the hold exerted by the pill over natural ovarian function.

As a footnote to this discussion, the FDA approved, in late 1998, a low dose estrogen formulation of the pill (norethinodrone acetate, 1 mg; ethinyl estradiol 20 mcg). Similar low-dose estrogen formulations are also now available in Australia.[66] The frequency of escape ovulation can only be expected to increase in this situation of reduction hormonal ingestion.

1.7 ENDOMETRIAL THICKNESS AND IMPLANTATION

Thus, the question arises: will a low dose pill, more inclined than not to permit escape-ovulation, increase the frequency of implantation failure due to a under-developed endometrium? The medical literature indicates that there is a critical thickness of the endometrium needed to sustain implantation of a human embryo.

Issacs *(Fert Steril,* 1996) reported that an endometrial thickness of at least 10mm or more, around the time of ovulation, 'defined 91% of conception cycles'.[67] Spandorfer *(Fertil Steril,* 1996) noted that 97% of abnormal pregnancies, defined as Fallopian tube lodgment or spontaneous abortion, had endometrial thickness of 8mm or less. [68] Shoham *(Fert Steril,* 1991) reported that a mid-luteal thickness of 11 mm or more 'was found to be a good prognostic factor for detecting early pregnancy' but no pregnancies were reported in an ovulation induction programme 'when the endometrial thickness was less than or equal to 7mm'.[69]

The mid-luteal phase of the menstrual cycle, around day 20, is referred to in the medical literature as the window of expected implantation.[70,71]

Gonen *(Journ In Vitro Fert Embryo Transf,* 1990) also reported that 'endometrial thickness was significantly greater in the group of patients who achieved pregnancy than in the group who did not'.[72] Implantation failure was associated with endometrial thickness of approximately 7.5mm, success with endometrial thickness of approximately 8.5-9mm.

These study results, which indicate a normative endometrial thickness of around 8.5mm for successful implantation, are central to any claimed interceptive/abortifacient capacity of the pill. Research findings from Rabe and co-workers (1997) underscore this point.

Rabe reported that study subjects who took the triphasic levonorgestrel/ethinylestradiol formulation had the highest percentage of follicular cysts with a diameter greater than $20mm^{/3}$ but they failed to develop a median endometrial thickness in excess of 6mm.[74] To recall, follicles of this size are 'thought to be associated with increased risk of escape ovulation'.[75]

The importance of these events is clear; follicles of a suitable size can develop in women taking the pill daily, but endometrial thickness has been shown to be underdeveloped. In the event of follicle rupture and release of an 'ovum', implantation of a human embryo would be greatly hampered. Rabe confirms this very point: '. . . the occurrence of pregnancy would be unlikely because accessory contraceptive mechanisms such as cervical hostility and endometrial suppression are usually in effect'.[76]

It must be pointed out that in this quote Rabe has falsely defined pregnancy as beginning at implantation. Pregnancy begins with the fertilization of the female sex cell (ovum) by sperm, the restoration of the full complement of 23 pairs of chromosomes and thereby the creation of a new human person.

Based upon these findings, a number of issues present themselves:

- An endometrial thickness around 8.5mm has been shown to be associated with successful implantation.
- Low dose triphasic formulations of the pill, the most popular in Australia, fail to completely stop follicular development, the precursor stage to the release of a female sex cell.
- Break-through ovulation is an event straining to occur, even with daily pill ingestion.
- If break-through ovulation were to occur, implantation might fail, because of an endometrium that is too thin.

It is important to note that these four observations exist independently of the impact of the pill on the various implantation factors involved in cell-signaling.

1.8 INTEGRINS

As the aforementioned research indicates, the last few years have seen a remarkable unveiling of the process of implantation of the human embryo into the uterine tissue. A large body of evidence now exists which demonstrates that the process of implantation, rather than being an accidental event dependent on chance, is in fact a multi-factorial, cascading bio-molecular,[77] physiological and hormonal event of spectacular intricacy, complexity, refinement and interdependence.[78] Implantation is not, as one might suppose, akin to two pieces of Velcro fortuitously touching and gripping together. Rather, implantation is, in every sense, as complex, and therefore susceptible to interference, as is the clotting mechanisms of the cardiovascular system.

Beside PAF, the interleukin system and other factors mentioned briefly in the introduction, the class of cell adhesion molecules known as integrins also play a critical role in successful implantation of the human embryo into the endometrium.

As the description of the molecule suggests, the role of integrins is to bind cells together. Etzioni has suggested that integrin facilitated cell adhesion is 'a process that is essential for anchorage' of cells to each other *(Lancet,* 1999).[79]

There are a variety of different types of integrins found within the body—one that plays an essential role in implantation is known as $\alpha v\beta 3$. The medical literature now contains many research papers demonstrating the vital role of this integrin in the process of binding the 5-7 day old human embryo to the endometrium (lining of the womb).

Somkuti and co-workers *(Fert Steril,* 1996) for example reported that integrins 'might prove useful as markers of normal endometrial receptivity'[80] because they have been shown to be absent in women with unexplained infertility and endometriosis.[81]

Similarly, Lessey *(Am J Reprod Immunol,* 1996) reported 'aberrant expression of this integrin is associated with infertility in women'.[82] Widra (*Mol Hum Reprod,* 1997) noted 'the absence of endometrial $\alpha v\beta 3$ during the critical period of implantation ... in women with unexplained infertility and endometriosis'.[83] Others had also commented on the absence or diminution of $\alpha v\beta 3$ in women with recurrent pregnancy loss[84] or unexplained infertility.[85]

Assessing the role of the pill, Somkuti (1996) compared endometrial sampling from women on the pill with samples from non-users and reported integrin expression 'to be altered grossly in OC users'.[86]

Complementing this work were the observations of Yoshimura (1997):'… a loss of normal αvβ3 expression is associated with primary infertility and milder forms of the disease. These observations suggest that this integrin plays a significant role in the implantation process'.[87]

Eric Widra and colleagues (1997), at Georgetown University investigated the role of physiological levels of estrogen and progesterone on the endometrial levels of αvβ3. They reported that estrogen caused a down-regulation in the expression of αvβ3,[88] an important finding in the light of the fact that 'expression of the αvβ3 integrin may, in fact, be necessary for normal implantation to occur.[8]

Castelbaum and co-workers *(J Clin Endo Metab*, 1997) reported the endometrial expression (presence) of αvβ3 was 'reduced by E2 treatment and further suppressed by E2 plus P...'[90]

These results indicate a link between the impact of hormones on the expression of integrins, and the role of integrins in implantation. Whilst the inter-relationship between hormones, integrins and implantation is not yet fully understood,[91] sufficient evidence exists to conclude that the inter-relationship is significant from the perspective of implantation. This is because implantation occurs only 'on or about day 20 of an idealized 28-day menstrual cycle' [92] and the αvβ3 integrin 'is expressed on endometrial epithelial cells only at the opening of the implantation window, on postovulatory day 6'.[93]

1.9 INSULIN-LIKE GROWTH FACTOR (IGF)

The IGF system is an important growth factor, playing a key role in the monthly development of the endometrium and in the process of implantation.[94] There are two subsets, IGF-1 and IGF-11. The first is believed to facilitate the mitotic action of estradiol [E2] in the endometrium, whilst IGF-11 'expressed abundantly in mid-late secretory endometrium, may be a mediator of progesterone action'.[95] Aside from this hormonal aspect, the most abundant expression of IGF-11 is in the columns of the invading trophoblast in the anchoring villi.

From this it can be seen that IGF has a promotional effect upon the process of implantation. But IGF is in turn regulated. 'The biological actions of IGFs are modulated by a family of binding proteins (IGFBPs). The demonstration of IGF and IGFBP transcripts [copying facilities] in pre-implantation embryos indicates that the influence of IGFs and IGFBPs in fetal development begins even prior to implantation'.[96]

Thus far, it can be seen that these factors have a key role to play in both the preparation for and process of implantation. As Han *et al.* have noted: 'Presumably, IGF-11 and IGFBPs are used for cell to cell communications between fetal trophoblasts and maternal decidual cells at the feto-maternal interface for placental development and/or function'.[97]

Against this background, the role of the hormones in the pill, particularly their influence over implantation, is important. A number of researchers have shown that the pill causes an increase in IGFBP-1 levels and a decrease in plasma concentrations of IGF-1.[98,99] More specifically, during the pill free-week 'IGFBP-1 was significantly lower on the medication-free day than on day 14 of the cycle . . . The short absence of exogenous estrogen and progestin during the medication-free week also affected IGF-1 levels, which were significantly increased'.[100]

The superabundance of IGFBP induced by the pill has, from an implantation perspective, significance. Giudice has reported that: 'IGFBP's bind IGF's with high affinity and, for the most part, inhibit IGF bioavailability to their receptors for action in their target organs'.[101] Thus, the supraphysiological levels of IGFBP, induced by the pill, may be detrimental to the process of implantation via an inhibitor action on the levels of IGF. Giudice highlights this point: 'IGFBP-1 has been shown to inhibit trophoblast invasion into decidualised endometrial stromal cultures, suggesting that this IGFBP-1 is a maternal "restraint" on trophoblast invasion'.[102]

Aside from the indirect anti-implantation effect of excessive levels of IGFBP upon IGF, IGFBP also has a direct, anti-attachment effect upon the human embryo. 'IGFBP-1 specifically binds to first trimester trophoblast and that it binds to the 'α5β1 integrin in trophoblast. Furthermore, it inhibits trophoblast attachment to fibronectin; another RGB ligand found in the placental bed.'[103]

In summary, the pill causes an increase in IGFBP levels, leading to a decrease in IGF levels. This may have a negative impact upon implantation. IGFBP also may have a direct effect at the level of trophoblast/endometrial integrin binding. More research is required to understand fully the roles of IGF and IGFBP. This represents a new, emerging field of research into the multitudinous factors involved in the process of implantation. Whilst the above research indicates that the pill facilitates anti-implantation endometrial environment, confirming evidence is yet to be found. Hence there exists a reasonable suspicion only, a point made by key researchers in the field.[104]

1.10 CONCLUSION

This discussion has had as its focus the multifactorial nature of embryo implantation. On occasion, this discussion has required detailed analysis of the relevant factors influencing the success of this event. Sometimes it is not possible to speak of these events, centred as they are on the maintenance of human life, without a certain measure of complexity and detail. To those readers who have struggled with this material I apologize.

This paper does not presume to be the final word on this complex and evolving branch of medical knowledge. New research appears almost monthly to illuminate further and sometimes confuse this emerging medical discipline. Nevertheless, I hope I have briefed the reader on issues related to the first right of all humans—the right to stay alive. Some may seek to discount the interceptive/ abortifacient capacity of the pill. For three reasons, this would be a scientifically precarious position to adopt.

First, I am of the view that the preceding evidence strongly argues the case in favour of the pill possessing an interceptive/abortifacient capacity. At the very least, the evidence is repetitive and circumstantial. Indeed, how more clear and straightforward could the issue be than the following statement from Eric Widra and colleagues? 'Demonstration of complimentary integrin expression on preimplantation embryos has further buttressed the argument that these molecules are important for the initiation of pregnancy'.[105]

Second, even researchers view as the new arena of 'contraceptive' research the interrelated system of implantation factors. Carlos Simon and colleagues (*Fertil Sterility*, 1998), after discussing the interdependent relationship between the interleukin-1 system, the avb3 integrin adhesion system and implantation, conclude by stating that the interleukin-1 system would be a promising new area of research apropos the development of new 'contraceptives'.[106] Given this sentiment, I am of the view that anti-interleukin chemicals will be the RU-486 of the next decade.

Third, and most tellingly, the abortifacient capacity of the pill is recognized by those who support abortion. Consider the following, taking from the *Guttmacher Report.* 'The best scientific evidence suggests that ECP's [emergency contraceptive pill] most often work by suppressing ovulation. But depending on the timing of intercourse in relation to a woman's hormonal cycle, they—as is the case with all hormonal contraceptive methods—also may prevent pregnancy either by preventing fertilization or by preventing implantation of a fertilized egg in the uterus' (my emphasis).[107]

Need any more be said?

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