# **Becoming one flesh**

Kathy Wallace

Women are at risk from sexual involvement with multiple partners. This can impact their health and increase the risk of miscarriage in pregnancy, low birth weight and dangerous diseases that have the potential to kill. Additionally, the intriguing, relatively recent discovery of DNA in the bodies of women, originating from the fathers of their children, has brought attention to an unsuspected biological closeness between a woman and her children, and between a mother and her spouse. This DNA, clearly distinct from the mother's, has been shown to persist in her body for decades after a pregnancy. Its presence not only may have health effects, but also exemplifies the deep biological union between a man and a woman, facilitated by the children they have together.

For this reason a man shall leave his father and his mother, and be joined to his wife; and they shall become one flesh" (Genesis 2:24).

There are rules about human relationships and reproduction entrenched in the Ten Commandments and elsewhere in the Bible. Scripturally, marriage is meant to be between one man and one woman, entered into for life.

In Jewish tradition the purpose of marriage is to procreate. Some women in the Bible were unable to bear children ever, like David's wife Michal; or until advanced in years, like Sarah, Hannah, and Elizabeth (and even then only by divine intervention). Or sometimes circumstance rendered them unable to bear children until years after marriage, like Tamar or Rachel. All would have struggled personally and socially for years, since the essence of Jewish womanhood was bound up with motherhood and the act of bearing children. Children were treasured, as demonstrated by the blessing given to Rebekah when she accepted the proposal of marriage brought to her—Genesis 24:60: "As they were leaving, they all blessed Rebekah by saying, 'Our sister, may you become the mother of tens of millions! May your descendants take over the city gates of those who hate them."

The church is the bride of Christ (2 Cor. 11:2), and He, as the perfect bridegroom, will return to acquire her. This symbol of marriage is exemplified by the notion of exclusivity.

#### Microchimerism: male DNA in women's bodies

There has recently been an explosion in the medical literature regarding microchimerism. In Greek mythology, 'chimera' were fire-breathing monsters with lions' heads, goats' bodies, and serpents' tails—i.e. made up from biologically different organisms (figure 1). 'Microchimerism' was first coined by a French mouse researcher to denote the coexistence, in the same organism, of two cellular populations derived from two different individuals.<sup>2</sup> In humans, cells derived from another person may persist in the body from diverse events, such as pregnancy, organ or tissue transplantation, or blood transfusion.<sup>3</sup>

Long known and widely reported is 'fetal microchimerism'—presumed fetal cells, including DNA, detected in women, which clearly have a different genetic make-up to that of the woman. In 1893 Georg Smorl described the presence of fetal cells in the maternal circulation, and reported on the importance of this in regard to pre-eclampsia.<sup>4</sup> His findings have been confirmed using advanced molecular techniques.<sup>5,6</sup> The presence of such genetically different cells was perhaps not quite as surprising as the fact that they persist in the maternal circulation and body for years. This is in contradiction to the traditionally held obstetric view, firstly that the placenta behaved like a barrier between maternal and fetal circulation, and secondly a more recent, widely held view, that fetal cells that gained entry to the maternal circulation would be destroyed by the maternal immune system, during or shortly after delivery. As claimed by Williams in 1907, "The foetal blood in the vessels of the chorionic villi at no time gains access to the maternal blood in the intervillous spaces".7 In the 1960s and '70s, fetal leukocytes, or white blood cells, were described in maternal circulation.8-10 Additionally, such cells were detected as early as at 15 weeks of gestation.<sup>11,12</sup>

So, how can fetal cells specifically be identified in maternal serum? Herzenberg et al. detected cells in maternal blood that carried the Y chromosome, from pregnancies with a male child.11 The fetus would have paternal 'antigens' or cell surface markers obtained from his father. Using an immunological technique, they were able to confirm, after the birth of the baby, that the infant's cells were indeed the same ones found in the mother's blood while she was still pregnant. The researchers knew that these women were carrying a male fetus as the women had undergone amniocentesis 11,13 at 15 weeks gestation to diagnose a possible fetal abnormality. Upon analysis, they were found to be carrying male babies. Fascinatingly, however, the study's authors accept that the male cells detected in the maternal circulation may have been acquired by means other than the pregnancy in question, in an earlier pregnancy or during a procedure such as a termination (abortion).9

### Bringing forth the fruit of one's womb ...

It is not by accident that behaviours stated in Scripture to be sinful, such as adultery and fornication, are also unhealthy. Many women know that their regular pap smears are designed to detect early changes in the cervical cells that may lead to cancer. But many are unaware that this disease is caused by a sexually transmitted virus called the human papilloma virus (HPV).<sup>14–16</sup> Condoms do not protect against infection by this family of viruses.<sup>17</sup>

Notably, where sexual partners commence a relationship while virgins, and remain together for life in an exclusive relationship (figure 2), the woman's risk of acquiring HPV and, subsequently, cervical cancer, is exceedingly low.<sup>18</sup> The Oxford Textbook of Pathology states, in regard to this, that women are at higher risk of cervical cancer by:

- having multiple sexual partners
- having a partner who has had multiple sexual partners
- · having sex at a young age.

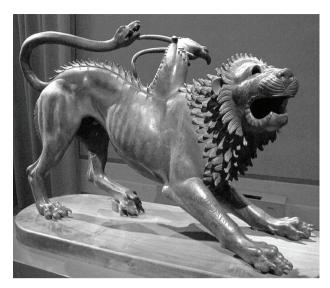
# Changing sexual partners and risks to subsequent pregnancy

A further risk to women from a change of sexual partner is illustrated by pregnancy-induced hypertension, which when severe was previously known as 'toxaemia', or 'pre-eclamptic toxemia', aka 'pre-eclampsia'. This can progress to full-blown eclampsia, an acute and life-threatening complication causing convulsions that can proceed to coma and even death of the pregnant woman and her unborn baby. First-time pregnancies, as well as the first pregnancy after a woman changes sexual partners, carry the greatest risk. 19,20 This indicates that passage of paternal antigen across the placenta may cause maternal disease.<sup>21</sup> This results from the woman's immune system's not being appropriately exposed to sperm from her partner for long enough for her immune system to recognise his 'foreign' tissues as acceptable.<sup>22–26</sup> Appropriately long exposure ensures that her immune system will behave tolerantly towards the embryo that results from their union, and that is half made up of his genetic material and half of hers.<sup>27–30</sup> It is understood that having protected sex by use of condoms, called the barrier method, or indeed using the 'withdrawal method' of protection against pregnancy, can lead to eclampsia risk in the first pregnancy.<sup>31,32</sup> A small trial involving less than 4,000 women also revealed an increased risk of pre-eclampsia in women using the oral contraceptive pill, but only when used for longer than 8 years.<sup>33</sup> In a small 2012 study, partner change was considered a significant factor in pre-eclampsia and low birth weight.<sup>34</sup> A larger study, in 2012, determined that paternal factors were critical in risk and occurrence of pre-eclampsia as well as low birth weight, but also declared the following weakness in their study:

"Although we had the opportunity to account for several important possible confounders that were not controlled for in earlier studies, we were not able to control for previous semen exposure, abortions and miscarriages or paternal characteristics." 35,36

Low birth weight and preterm deliveries were also associated with prior termination of pregnancies, or abortions,<sup>37</sup> and longer-term consequences for health.<sup>38</sup>

There is presently good evidence to suggest that the immune tolerance generated in the woman by unprotected sex with her husband results in successful and complication-free pregnancy outcomes. This outcome has been linked not to coitus alone but to sperm exposure. The presence of sperm in the woman's body provides priming events for exposure to the female T cell lymphocytes resulting in maternal immune tolerance to the paternal antigens. 39,40 These T cell lymphocytes, thus reprogrammed, recognise the paternal antigens in the conceptus and facilitate implantation rather than attack the 'foreign' cells. There is burgeoning medical literature demonstrating that a lack of immune tolerance has been linked with severe complications, including risk of miscarriage, preterm labour,41 pre-eclampsia,42 preterm rupture of membranes (that is, the mother's waters breaking prematurely), placenta abruption (the placenta coming away from the uterine wall prematurely), intrauterine growth restriction (a baby who will not achieve normal weight and size), and HELLP syndrome, 43 (haemolysis, elevated liver enzymes, and low platelets—a devastating disease described as a worse form of eclampsia).44,45 The significance of maternal immune intolerance is further illustrated by the higher risk of preeclampsia and miscarriage in pregnancies from in-vitro fertilization, or IVF.46-48



**Figure 1.** In Greek mythology, 'chimeras' were fire-breathing monsters with lions' heads, goats' bodies, and serpents' tails—i.e. an amalgam of biologically different organisms.

### Prenatal screening and risk of sex selection

The applications of such prenatal detection of fetal cells led to the development of screening tests, 49,50 the refined versions of which are used today to assess the risk of chromosomal abnormalities in a pregnancy.<sup>51,52</sup> The underlying rationale of this 'first and second trimester screening' is to give a couple, at worst, 'justification' to terminate a pregnancy (i.e. kill their baby) if it is carrying abnormal chromosomes, or, at best, advance warning to prepare for a possible abnormal outcome in their progeny. A disturbing reality of the newer breed of prenatal-screening blood tests, presently being offered by numerous pathology laboratories in Australia, is the potential for sex selection; that is, termination of a pregnancy based on the sex of the baby. It is also reported that finger prick blood test kits are available via mail order for sex determination of an unborn child. Costa et al. were able to detect fetal DNA in the maternal circulation at 42 days and had no false negatives in detecting pregnancies with male babies, 53 which is a reflection of the accuracy of such tests.

## Two-way traffic

This area of molecular biology, while an exciting frontier in medicine, leaves numerous unanswered questions as well, such as the significance of a woman's mother's microchimerism detected in women with healthy pregnancies versus this form of maternal grandmother-microchimerism being relatively absent in women with pre-eclampsia. 54,55 Also, while fetal cells migrate into the maternal circulation, maternal cells similarly enter the fetus. 56 It has been noted that maternal cells in the fetal circulation also perform

immune-modulating functions and cause suppression, or tolerance, in the fetus towards maternal antigens. 57,58 It is critical that immune suppression towards maternal antigens occurs without over-suppression of the fetal immune system—a balance here is important.<sup>59</sup> The significance of this materno-fetal microchimerism seems related to and enhanced by breastfeeding and also may cause tolerance towards infective agents, such as HIV acquired via vertical transmission that is, from mother to child. Recent research, including that in animal models, has revealed that maternal cells in the fetal circulation occur in all pregnancies, and can be detected as early as 4 weeks and 5 days. Other reports have indicated that maternal cells gain access to the fetal circulation as early as 9-10 days post-conception.<sup>60</sup> Thus, as described above, materno-fetal microchimerism provides necessary immune regulatory functions, akin to a military force undertaking measures to minimise casualties by friendly fire. It seems that maternal cells gain entry via the placenta in all pregnancies and result in tolerogenic fetal immune responses to non-inherited maternal antigens. A mother gains the advantage from feto-maternal microchimerism by the potential protection afforded by a supply of fetal cells that are pluripotent (that is, behaving like stem cells), and that may aid cellular repair. 61,62

## How do fetal cells gain access to maternal circulation?

The exact mechanism by which fetal cells gain access to the maternal circulation requires further clarification. However, increased trafficking of fetal cells into the maternal circulation can occur in a variety of events such as external cephalic version,<sup>63</sup> where a baby positioned the wrong way in the uterus is turned manually by an obstetrician; as well



**Figure 2.** Sexual intimacy and bearing children result in becoming 'one flesh' through shared DNA.

as miscarriage and abortion.<sup>64</sup> In an abortion, destruction of the placenta may be the means by which fetal cells gain entry into the maternal circulation.<sup>65</sup> This has been disputed, though, in an animal model where complete hysterectomies rather than abortions were performed on pregnant mice, and fetal DNA was, nonetheless, detected in maternal tissues, leading the authors to speculate that fetal microchimerism occurred prior to placental implantation.<sup>66</sup> Another animal model has demonstrated that should the exposure of fetal antigens to the maternal circulation occur via disruption or intervention in the fetus, as in the case of pre-natal fetal surgery, there is an increased risk of fetal demise from activation of maternal T lymphocytes and an immunogenic reaction to the fetus.<sup>67</sup>

# Male microchimerism in women who were never pregnant with male babies

Surprisingly, women who have never been pregnant with sons have also tested positively for male fetal microchimerism. A 2005 study set out, as a secondary objective, to gauge whether male microchimerism detected in women could possibly have arisen from sources other than pregnancy with a male child. It is suspected that persistent male DNA may be present in some women from a twin pregnancy, an older brother via maternal transfer, unrecognized miscarried pregnancies and sexual intercourse.<sup>68</sup> This study also reported a higher rate of fetal microchimerism in women that had had elective abortions. Sexual intercourse as a means of male DNA transfer has been considered as possible in other studies as well, where women who have never been pregnant are found to be positive for male microchimerism.<sup>69</sup> The authors suggested that the term 'fetal' DNA be replaced by 'exogenous' DNA, and that the specific origin of all male DNA in women be further investigated. It would be interesting to record whether or not 'male DNA' is limited to detection of a Y chromosome, or whether there is DNA specific to a particular male sexual partner.

#### Disease states associated with microchimerism

Microchimerism has been detected in autoimmune diseases, cancers, and endocrine disorders. <sup>70</sup> Persistent fetal microchimeric cell lines have been known to endure in maternal bone marrow and are postulated to seed into maternal tissues, being detected as long as 27 years after the birth of the baby. <sup>71</sup> Thyroid diseases are linked to microchimerism, and fetal microchimeric cells are absent from healthy thyroids in some reports. <sup>72–74</sup> Likewise, microchimerism has been investigated in different autoimmune disorders, such as systemic sclerosis, systemic lupus erythematosus, autoimmune thyroid diseases, as mentioned above, primary biliary cirrhosis and juvenile inflammatory myopathies. <sup>75</sup> However, microchimerism is also detected in the thyroids,

lungs, skin, lymph nodes, kidneys, livers and hearts of healthy women in other reports.<sup>76–78</sup>

Male microchimerism has been detected in multiple brain regions in women with and without Alzheimer's disease. Since Alzheimer's disease rates are higher in women that have had children than those that have not, it was expected that male microchimerism may be higher in women with Alzheimer's disease. Unexpectedly, precisely the opposite results were found; male microchimerism was higher in women without Alzheimer's disease. However, as the authors explain, their sample size was modest, and further work in this area is needed. Of interest, the oldest woman in whose brain male microchimerism was detected was 94 at the time of her death (figure 3).

Male microchimerism was also detected in the livers, diseased or normal, of females, whether they had had male offspring or not—and also in the livers of deceased female fetuses. Forty-six liver samples from 29 women, 6 female children, and 11 female fetuses were screened for the Y chromosome via polymerase chain reaction (PCR) assay and fluorescent in situ hybridization (FISH). The Y chromosome was detected in 5 of 6 children, 7 of 11 fetuses, 3 of 9 women with normal liver, 7 of 10 women with chronic hepatitis C, 5 of 6 women with acute liver disease during pregnancy with male offspring, and 2 of 4 non-pregnant women with fulminant hepatitis. The presence of male microchimerism was higher in diseased livers than unaffected ones. The authors suggested:

"The presence of male cells in the liver of female children and fetuses is probably due to the transplacental transmission of fetal cells preexisting in the mother and acquired either from previous pregnancy with male offspring or during the mother's own fetal life." 82



**Figure 3**. Cells exchanged between mother and baby during pregnancy can persist for decades after birth.

#### Fetal microchimerism as a biomarker for disease?

Can the absence or presence of fetal microchimerism be used as a biomarker for disease, such as breast cancer? A series of valid reports supports this possibility. A 2013 study is the sixth of its kind that demonstrates the possibility that microchimerism can yield a reliable marker for breast cancer risk assessment. The researchers corroborated the existing understanding that women with little detectable microchimerism are at a higher risk of in situ breast cancer.<sup>81</sup>

While protective in breast cancer, male microchimerism was associated with a higher risk of bowel cancer. 82 Thus, the effects of microchimerism on the breast are quite opposite to those on the bowel. The study authors stated that microchimerism was highly relevant to later cancer development.

In a review article regarding microchimerism and its potential beneficial effects, the authors state:

"Much of the information that is currently available derives from studies of association, and causation is unknown. It is difficult to know in studies of human biopsy or autopsy samples whether microchimerism is an active participant in damage, an incidental marker of concurrent processes, or a potential contributor to repair. Some studies have found evidence of fetal cell differentiation in maternal tissue suggesting they may be involved in tissue repair in a variety of different organs."83

# Children by multiple partners resulted in higher maternal mortality

Naturally, if fetal microchimerism can impact maternal health, then how does fetal microchimerism from different partners impact maternal health? Olsen *et al.* investigated health outcomes between women who had pregnancies by one partner and women who had pregnancies by more than one partner.<sup>84</sup> In this 2003 paper the authors acknowledge that a study such as theirs was prone to methodological difficulties due to problems with adjusting data for social differences in their study groups. They stated:

"Women who had children with more than one partner had a higher relative mortality rate, which was even higher if she had children by more than two partners. This finding persisted after excluding unnatural deaths and did not depend on time from exposure. Although some of the findings were adjusted for parity, age and social factors, it is highly unlikely that these large differences are entirely related to microchimerism. The study shows that caution is needed when studying health effects of procreation with multiple partners."

The authors also said that they could not believe that such a large difference existed between the mortality rates in the women they studied based on whether the women had children by single or multiple partners. They state:

"It is hard to believe that these major differences in mortality are all related to induced immunological changes including microchimerism of a multiple partner origin. More likely the differences reflect the impact of social factors, lifestyle, and stress related to changing partners and all the rest that goes with unstable social and personal conditions. Reproducing with several partners seems to be a risky matter, but most of the risk probably belongs to the domain of risky behaviour in general rather than microchimerism. Microchimerism could have causal importance for several diseases, which could lead to death after several years of follow-up time, but the microchimerism theory is not expected to manifest itself within the first years of follow-up, as we saw [emphasis added]."

Another Danish study in 2004 set out to determine if there was a cancer risk associated with women having children with multiple partners. They detected a more than 50% higher cancer rate for women that had children by more than one partner. 85 They stated that they found a higher risk of cervical and uterine cancers, as expected; and unexpectedly, they found that breast and ovarian cancers were not significantly lower in the group of women that had children with more than one partner. The results of previous studies detailing protective effects of multiple partners on risk of breast and ovarian cancer were not replicated in this study.86 The findings of this study were similar to an earlier Swedish report from 2001, where no reduction in breast cancer risk was found in women bearing children with more than one partner; in fact the authors had reported a slightly elevated risk of cancer in the group of women that had children by two or more partners. 87

## A challenge for feminists

Feminists are confronted with a challenging situation where, in the face of their struggle for autonomy, and for characterisation as individuals without reference to their biological capacity for child bearing, they will now be forced to accept being inextricably linked biologically to not only their children, including their aborted babies, but also to their children's fathers.<sup>88,89</sup> There is presently no evidence that DNA from women can engraft into their husbands via sexual intimacy.

# Donated eggs and embryos in assisted reproduction

In married couples with female infertility, the husband's sperm may be utilized for creation of an embryo derived with the ovum obtained from another woman. The ensuing pregnancy can result in fetal microchimerism and the foreign

female DNA may embed in the mother/recipient. Women becoming pregnant with donor eggs fertilized by their husbands have been found to have male microchimerism for as long as 9 years in one study, implying that the foreign fetal DNA avoids detection by the mother/recipient.<sup>90</sup>

By the same token, donated embryos may constitute a perplexing challenge for couples in terms of the spousal one-flesh union in marriage, as the fetus delivers its paternally derived DNA into the mother's body, thereby colonizing her body with the genetic heritage of the non-spouse father.<sup>91</sup>

Fetal microchimerism also forces bioethical considerations in gestational surrogacy. Loike and Fischbach quote a case where a child was born with a maternally derived leukaemic tumour in her cheek, highlighting the risk of diseased maternal cells migrating into the fetus and causing disease. Pa Scellular and DNA traffic is two-way, a surrogate mother's DNA is likely to embed in the biologically unrelated baby that she carries, and the baby's DNA is likely to embed in her.

## Implications for lesbians using donor sperm

This process of fetal microchimerism also has implications for lesbians using donor sperm to facilitate procreation. Presently, such women may be unaware that donor male DNA will be indelibly embedded within them, enshrined vestiges of the biological process resulting in children, that requires a man and a woman, as ordained by God. Scarnecchia has said:

"The man whose embryo implants in a woman literally becomes one-flesh with her as fetal chimeric cells bearing his genetic heritage differentiate and colonize her organs and tissues, for better or worse, till death do they part. ... Because it has its causal origin in the sexual act, the fetal chimeric stem cells containing male DNA of its father's lineage that differentiates into the tissues and organs of the mother's body signifies an on-going sexual penetration of the woman's body by the paternal genetic heritage of the child."91

#### Conclusion

Having the DNA of a separate individual integrated into one's body for life, conveyed via the process of procreation, emphasises the depth of the intimacy achievable for a male and female union.

Following God's instructions contained in His Word regarding sexual behaviours results in better health outcomes for women. This is as expected since God is the author of life and He has said, in John 10:10, "The thief comes only to steal and kill and destroy. I came that they may have life and have it abundantly."

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