BIOCHEMICAL PREGNANCIES AND THEIR MANAGEMENT

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SUMMARY

There is little information in the literature about biochemical pregnancies (BP). However, BP (a pregnancy that regresses before imaging with ultrasound) is a significant problem in IVF and recurrent miscarriage clinics. The incidence of between 13-22% of pregnancies may be confounded as today's sensitive pregnancy tests may detect endometrial, pituitary, or phantom hCG. A false positive result may also follow extraneous hCG administered in an ART cycle. Hence, the author has suggested a rising hCG level at two consecutive tests as a definition and that one raised hCG level should be known as a raised isolated hCG level. The etiology remains unclear. Embryonic aneuploidy, thinned endometrium, sperm defects, and defective angiogenesis have been suggested. Additionally, several biochemical pregnancies are early ectopic pregnancies that fail to develop further.

We see a subsequent live birth rate of 53% in untreated patients with two or more biochemical pregnancies. However, our team treats recurrent BP's as recurrent pregnancy loss (RPL) as suggested by ESHRE. However, treatment to prevent further BPs is empiric, with no evidence in the literature. The author uses hCG supplementation to enhance implantation. 61 of 87 patients (70%) with >2 biochemical pregnancies and 12 out of 14 patients (86%) with >4 biochemical pregnancies delivered with hCG supplementation. These figures compare favorably to the 53% live birth rate with no treatment, but power analysis shows that 228 patients would be required to show statistical significance. The author has used IVIg on 20 patients with >5 biochemical pregnancies, with 50% terminated as live births. However, the results may be confounded as the previous biochemical pregnancies may have been early ectopic pregnancies, and the subsequent pregnancy intra-uterine.

If a biochemical pregnancy becomes persistent and hCG levels fail to fall, methotrexate may be required, as in early ectopic pregnancies.

Keywords: Biochemical pregnancy (BP), hCG levels, in vitro fertilization (IVF), recurrent pregnancy loss (RPL), ectopic pregnancy, implantation enhancement, methotrexate treatment

Biochemical Pregnancy

The most common definition of a biochemical pregnancy (BP) is a positive βhCG test with no pregnancy on ultrasound. The most recent terminology is from the European Society of Human Reproduction and Embryology (ESHRE) in 2015.[1] The classification is based on previous definitions. If there is a decreasing βhCG level and no localization of the pregnancy on ultrasound, if performed, the pregnancy is known as a non-visualized pregnancy.[2] If no ultrasound has been performed, the pregnancy loss has been called a "biochemical pregnancy."[3] If the pregnancy resolves spontaneously after expectant management, it is known as a resolved pregnancy of unknown location after expectant management.[4]

However, in in vitro fertilization (IVF) programs, low levels of βhCG may be diagnosed and interpreted as a biochemical pregnancy. Consequently, past definitions include βhCG levels of 10-1000 IU and a rising level.[5, 6] An alternative nomenclature suggests raised isolated hCG levels and biochemical or non-visualized pregnancy if the hCG level rises without extraneous hCG administration.

It is questionable whether BPs should be recognized as pregnancies, early miscarriages, or implantation failures. The American Society of Reproductive Medicine (ASRM) distinguishes BPs from clinical pregnancies and does not recognize BPs as miscarriages, as raised isolated hCG levels may peak and rapidly fall, and there may be no delay in the onset of the next menstrual period. Additionally, as BPs cannot be localized, every biochemical pregnancy is a pregnancy of unknown location (PUL). PULs may be early ectopic pregnancies. The ESHRE recognizes BPs as miscarriages, partly based on Kolte et al's[2] work that each non-visualized pregnancy loss reduces the chance of a subsequent live birth by 10% (RR, 0.90, CI 0.83; 0.97), similar to the risk conferred by each additional clinical miscarriage. The author runs a dedicated clinic for women with recurrent pregnancy losses. In this clinic, there are many women with BPs and recurrent BPs. Our experience is similar to Kolte's[2] experience. Hence, the author does classify BPs as early miscarriages if there is a rising hCG level.

Raised Isolated hCG Levels

The mRNA for hCG has been detected in 8-cell embryos. hCG from 7 days after ovulation[7] and can be used clinically from 9 days after the LH surge. A positive hCG after 12 days is usually indicative of pregnancy. However, present tests are so sensitive that phantom, endometrial, or pituitary hCG can be detected. A low positive hCG does not invariably mean that trophoblastic hCG is present. Additionally, some tests use animal antibodies raised to hCG. If the patient harbors anti-animal antibodies after exposure to the same animal used in the test, there may be a false positive result. If hCG is used for ovulation induction, it may still be present after 12 days. Van Der Weier et al.[8] showed low amounts of hCG as a contaminant in hMG, and Kol[9] showed hCG as present in Corifollitrophin α. Intra- and inter-laboratory variation may also lead to false positive results. These low levels of hCG are raised isolated hCGs, not biochemical pregnancies.

Incidence

The prevalence of biochemical pregnancies has been reported to vary between 13-22% in fertile patients.[10,11] Isolated elevated hCG levels have been reported in 4% of Liu et al.'s series.[12] In the infertile population, the incidence has been reported to be 14-18%, which is not higher than in the fertile population.[13,14] A higher incidence has been reported in IVF patients (22-31%) compared to the general infertile population.[15,16] However, the incidence remains stable across all age groups and does not increase with age.[17]

Causes of Biochemical Pregnancies

The cause of biochemical pregnancies may depend on the embryo or the mother.

Embryo Causes:

hCG is essential for human implantation. The hCG produced at the start of pregnancy is mainly the hyperglycosylated form hCG-H.[18,19] hCG-H is autocrine in nature, created by the cytotrophoblast to drive invasion of the syncytiotrophoblast. According to Sasaki et al.,[20] only 8 of 36 biochemical pregnancies produced >40% hCG-H on the day of implantation, compared to 100% of pregnancies terminating at term. Alternatively, if implantation is delayed, a slow rise in hCG may indicate abnormal embryonic development, which may have occurred after implantation due to chromosomal or other embryonic factors.[21]

As recurrent implantation failures and miscarriages are often due to embryonic aneuploidy, it has been assumed that biochemical pregnancies may be due to a genetic aberration. Troncoso et al.22 reported a case-control study in which 62 patients underwent PGT, and their BP rates were compared to 62 patients undergoing embryo transfer on day 3 or 62 patients on day six after ovum pickup. The incidence of BPs was approximately 25% in all three groups. Hence, embryonic chromosomal aberrations were not the cause of BPs in most patients.

Maternal Causes:

Endometrial thickness has been reported to impact biochemical pregnancies. In Dickey et al.'s report,[23] BPs were found in 21.9% (7 of 32) of pregnancies if the endometrial thickness was less than 9 mm on the day of hCG administration in women undergoing ovulation induction, but none of 49 pregnancies when the endometrial lining was more significant than 9 mm. Hence, a thin endometrium may not allow proper invasion by the trophoblast and inappropriate placentation. Additionally, hCG secretion by the invading trophoblast may be negatively modulated by endothelin-1 (ET-1) or PG F2α found in the endometrium.[24] Oxidative stress can also enhance hCG levels while not allowing necrosis and apoptosis of the trophoblastic epithelium.[25]

Implications of Biochemical Pregnancies

The occurrence of a biochemical pregnancy is psychologically distressful for both partners. There is joy in achieving a pregnancy after prolonged infertility, only to have that happiness dashed by pregnancy loss. Hence, the stress associated with biochemical pregnancies has led to patients leaving IVF programs.[26]

The occurrence of a BP is a negative predictor for subsequent pregnancy outcomes, as BPs have higher recurrent BP and miscarriage rates.[27,28] In cases of exclusively recurrent biochemical pregnancies, the risk of ectopic pregnancy has been reported to be 27%.[29] However, 6% to 20% of women with sporadic BP have an ectopic pregnancy.[30]

Management

BPs may be non-viable or present with persistent raised hCG levels. In some cases, methotrexate (MTX) may be required to induce trophoblast regression. In ectopic pregnancy, MTX is associated with a 67-94% success rate. Side effects such as stomatitis, gastrointestinal distress, dizziness, neutropenia, reversible alopecia, abdominal pain, and vaginal bleeding or spotting may occur. After recurrent biochemical pregnancies, there is insufficient information from the literature to formulate guidelines for management. Below are some suggestions based on the author's experience, which are not evidence-based.

If there is one isolated BP, the author believes there is little need for active treatment. If there are two consecutive BPs, there is still little need for active treatment. However, ESHRE regards two BPs as two pregnancy losses and, therefore, can be assumed to support treatment to prevent recurrence. If there are three or more BPs, the author treats the patients as if there were three or more miscarriages. Our database contains the details of 87 patients with two or more BPs who did not receive active treatment in the index pregnancy. There were 61 subsequent live births (70%), not significantly different from 22/41 (54%) in the control group.

Power analysis shows that 410 patients are required to show statistical significance.

Specific Medications (Author's Experience):

There is little information on various drugs used to improve the live birth rate. As stated above, hCG-H accounts for 90% of the total hCG in the first two to three weeks of pregnancy when invasive trophoblast activity is highest.[18,19] Hence, a luteal dose of hCG is often administered in IVF practice to enhance implantation. Theoretically, hCG-H may prevent pregnancy failure at the time of implantation. However, hCG-H is patented and not commercially available; therefore, generally, commercially available hCG can be used instead. hCG prevents further miscarriages in recurrent miscarriage.[31] The author has used hCG supplementation in 34 patients with three or more BPs. 26 subsequent pregnancies terminated as live births (76%). However, the numbers are too small to determine if this 76% live birth rate significantly differs from the 61% seen in the control group (11 live births in 18 pregnancies). The author has used intravenous immunoglobulin in patients with five or more BPs. Ten live births were achieved in 20 pregnancies (50%).

CONCLUSIONS

Much more data is necessary on biochemical pregnancies. Databases must be combined to increase the number of patients available for assessment. One possible source of "big data" is the Society for Assisted Reproductive Technology (SART), but BPs should be reported as BPs and not early pregnancy losses. Detailed histological studies need to be performed on failed pregnancies. It is essential to understand if hCG-H levels are deficient and, if so, if hCG-H may prevent BPs.

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